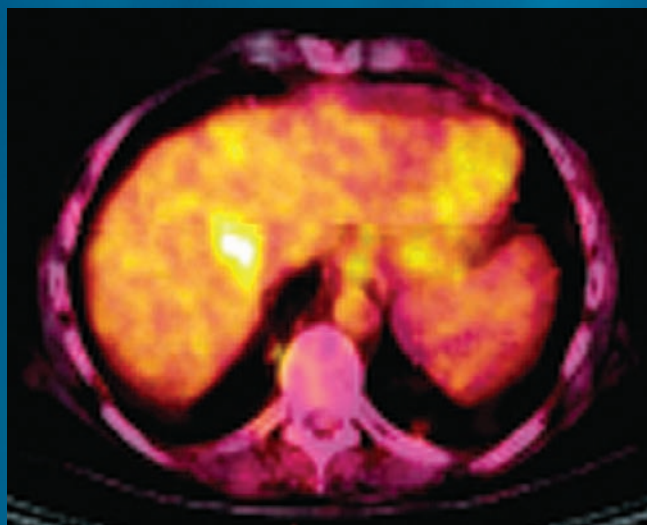
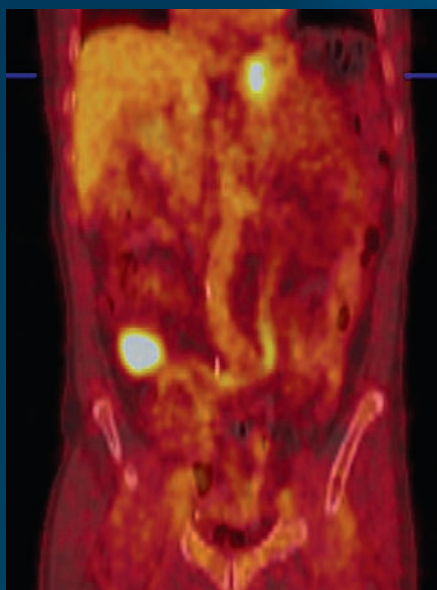


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Positron Emission Tomography Computed Tomography

A Disease-Oriented Approach



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healthcare

Edited by
Elissa L. Kramer
Jane P. Ko
Fabio Ponzio
Karen Mourtzikos

Title Page To Come

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Elissa L. Kramer

*To Jay, Rachel, Aaron, Daniel, David, and Nikki with thanks
for their support and forbearance*

Jane P. Ko

To my husband, Agustín, and my daughters Ana Maria and Isabel

Fabio Ponzo

To my wife, Lucia, and my parents

Karen Mourtzikos

To Carlos, always, and with gratitude to my family

Foreword

PET/CT epitomizes a marriage made in imaging heaven. The ability of PET to image cellular metabolism combined with the anatomic detail of CT represents a transformational approach to imaging neoplasia and other diseases. The task of PET/CT image interpretation is also challenging. This stems from the need to be highly skilled in both nuclear medicine and body/brain imaging. The impact of this technology has been enormous in cancer, Alzheimer's disease, and epilepsy; now representing an integral component of the standard workup and management of these patients.

Editing a book and writing definitive chapters on particular subjects is not a comfortable task. It is most difficult to decide what not to emphasize. I believe Drs. Kramer, Ko, Ponzo and Mourtzikos and their co-authors have succeeded magnificently in capturing the essentials of the particular topics. The book conveys a definite perspective from those engaged in a busy clinical practice seeing a spectrum of disease entities. All of the authors have enormous experience in PET/CT as well as being highly skilled clinicians. Readers will gain a firm grasp of the subject matter that is pertinent to the applications of PET/CT in the clinical milieu.

I have been impressed with the growing list of purposes for which PET/CT has been recommended and approved. Such adoption indicates the vitality of this unique device. Obviously there will be continued growth and refinement in the field. My intuition tells me this will be the first of many subsequent editions.

Position Emission Tomography-Computed Tomography: A Disease-Oriented Approach will serve as a most useful and lucid reference for those engaged in learning and using PET/CT. As the former Chairman of Radiology at NYU I am particularly proud that the majority of PET/CT expertise in this book springs from the well of outstanding individuals in our Radiology Department. I would like to toast the contributors for their outstanding work and am honored to be acquainted with them both professionally and personally.

Congratulations and best wishes!

*Robert I. Grossman, M.D.
Dean and CEO,
New York University School of Medicine*

Preface

The introduction of dedicated instruments to perform functional positron emission imaging in combination with CT opens an extraordinary vista for the diagnostic imager. Suddenly, we have been confronted with closely registered images that permit the reliable, and almost instantaneous, fusion of anatomy with metabolic information. Findings on PET may be explained now by their relationship to normal anatomy or may take on greater significance because of abnormal CT findings. CT findings may now be recognized, more thoroughly considered, or summarily dismissed based on their metabolic attributes. Relatively inconspicuous findings on PET take on greater meaning when they relate to identifiable structures. While this dual modality imaging provides a great many answers, inevitably combined PET/CT raises new questions and creates new challenges for us. For the physician coming from a nuclear medicine/PET background, the detailed body of knowledge developed over the past 20 years in chest and body CT must be mastered to better clarify the meaning of metabolic activity and thereby extend the clinical utility of PET. For the CT radiologist who needs to wield the metabolic tool of PET with facility and expertise, an in-depth understanding of the subtleties of functional imaging both in terms of patient preparation and image interpretation is necessary.

This book aims to provide a thorough understanding of the technical demands involved in combining CT and FDG PET: patient preparation, acquisition techniques including potential pitfalls and limitations, and the basics of instrumentation and physics needed for developing cogent technical approaches. Technical advances and controversies including the use of CT contrast and, when clinically relevant, newer radiopharmaceuticals (beyond the most clinically available ^{18}F -2-deoxy-fluoro-D-glucose or FDG) are addressed briefly.

The *raison d'être* of this work is to offer the practicing nuclear medicine physician/radiologist a thorough understanding of the clinical application of these dedicated PET/CT scanners to oncology and neurologic disease. Whenever possible, the place of PET/CT in the diagnostic algorithm is explored and with it the particular information provided by both FDG PET and CT for the analysis of a particular diagnostic problem. When clinical questions remain even after PET/CT, further answers may come from other anatomic or functional imaging. We explore these strategies when there is evidence to support their use.

In this context, we have attempted to provide a comprehensive, disease-oriented approach to PET/CT. We review the diagnostic setting in which PET/CT will prove

most valuable, the PET findings, literature-based evidence for utility, applications, and limitations to each disease and specific clinical settings related to that disease. In each section we have attempted to include CT findings that will bear on the PET interpretation and vice versa. It is our hope that this book will provide a practical, comprehensive guide for the imagers on the front line of clinical diagnosis and management of cancer and central nervous system diseases.

As we think about the genesis of this book, first and foremost we should acknowledge the support and enthusiasm for PET/CT of our chairman, Dr. Robert Grossman. We thank our radiology and clinical colleagues for their patience, questions, and feedback. We have learned from them continuously. We are also grateful for the efforts and untiring interest of our fellows and residents and for their contributions to this text. The book would have been impossible without the input of our team in the Diagnostic Imaging Department at the NYU Clinical Cancer Center. They have been enthusiastic, creative, and expert technologists in this adventure: Barbara Moczulska, Veronica Briglall, Gregory Vaynshteyn, and Lewen Cao. They taught each other their respective modalities and helped us with the ins and outs of putting PET and CT together; the nurses Christine Compton Perez and Maureen Stasi who have skillfully guided our patients and us through dietary dilemmas, diabetes medications, and contrast issues; and Emilio Vega, whose technical expertise has repeatedly weighed in when we were uncertain about the best way to adapt our CT protocols. Our thanks also to Martha Helmers and Tony Jalandoni, who helped us with the images for this book with their ever-present patience and attention to detail.

Elissa L. Kramer

Jane P. Ko

Fabio Ponzio

Karen Mourtzikos

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Technical Aspects of CT in Practice

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INTRODUCTION

As improving computer tomography (CT) technology is integrated into positron emission tomography (PET)/CT scanners and the advantages achieved by combining CT and PET are better appreciated, the restrictions for CT acquisition during PET/CT studies have decreased. Troubleshooting while performing PET/CT scans requires an understanding of both CT and PET technology. A working knowledge of CT technology, quality control procedures, parameters affecting image quality, and the technical factors influencing patient exposure is essential to perform satisfactory PET/CT studies, while maximizing patient safety and minimizing radiation exposure.

CT TECHNOLOGY

CT technology has improved dramatically with the development of helical and, more recently, multidetector CT (MDCT) capabilities. Prior to helical imaging, direct axial CT acquisition was performed, which entails a 360° rotation of an X-ray beam around the patient while the gantry table remains stationary at a z-axis position. Subsequently,

table translation along the z-axis occurs, and then the sequence of spiral acquisition and table translation is repeated multiple times to cover the desired anatomical structures in the z-axis. Helical CT technology involves continuous motion of the gantry table while the X-ray tube continuously rotates, producing a helical motion of the X-ray beam through the length of the patient imaged. With single-detector helical scanners, the thickness of the X-ray beam determines the slice thickness that is obtained (Fig. 1). MDCT scanners have multiple detector rows in the z-axis, and therefore the X-ray beam in the craniocaudal dimension is wide (1–3). The information received at the detectors can be divided into thinner axial sections secondary to the multiple detector rows (Fig. 2). MDCT scanners are currently up to 64 rows or channels of information, with greater capabilities in the near future. Detector configurations vary according to the manufacturer. Four- and 8-MDCTs can have a fixed array detector, comprising detector elements of the same size in the z-axis, or an adaptive array design, composed of detector rows with varying z-axis lengths (4). Therefore, in addition to thinner sections, greater z-axis coverage, decreased motion artifact, or combinations of these can be acquired using MDCT imaging.

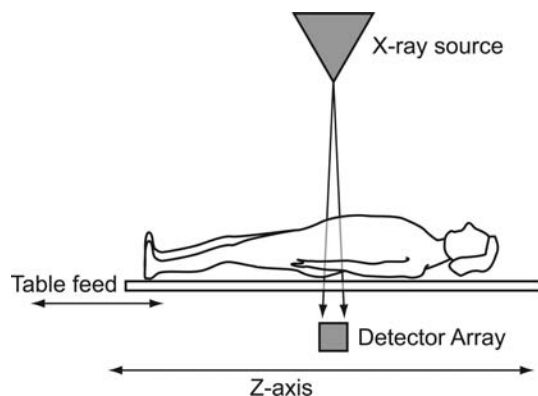


Figure 1 Single-detector CT. The detector array has one detector row in the z-axis. The thickness of the section depends upon the beam collimation.

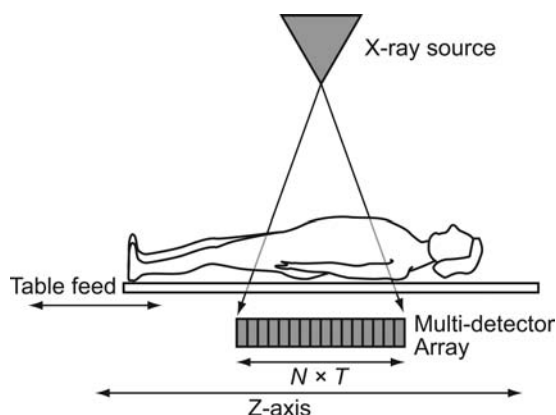


Figure 2 Multidetector CT. The detector array of an MDCT scanner comprises multiple detectors in the z-axis. Given the multiple detectors, a wide fan-shaped radiation beam can be segmented to obtain multiple thinner sections.

CT QUALITY CONTROL

The CT performance of a PET/CT scanner should be assessed in accordance with the American College of Radiology (ACR) guidelines for CT. The objective of a CT quality control program is to maintain optimal image quality and safety so that the radiation used is properly calibrated and regulated. The parameters that are tested in a quality control program pertain to image quality, safety, and mechanical aspects (Table 1). Image quality factors assessed include image noise and uniformity, spatial resolution, Hounsfield unit calibration, scan plane alignment with the laser, and imaged slice thickness. Parameters that evaluate safety and radiation dose include the in-air CT dose index (CTDI) and the irradiated dose profile. When PET/CT is involved, communication between the CT and PET gantries and alignment between the PET and the CT acquisitions must also be assured.

Table 1 CT Quality Control Parameters

	Parameter	Frequency ^a
Safety	CTDI	Semiannually ^b
	Irradiated dose profile (slice thickness)	Semiannually
Image quality	Image noise	Daily
	Image uniformity/homogeneity	Daily to monthly
	Spatial resolution (MTF)	Monthly
	Hounsfield unit/CT numbers	Daily (water)
	Imaged slice thickness	Monthly to semiannually
	Scan plane light alignment	Monthly to semiannually
Mechanical	Couch plane movement	Monthly to semiannually
PET/CT	Gantry communication	Daily
	Gantry alignment	Daily

^aAlways repeated with hardware or software changes.

^bPerform more frequently until stable.

Abbreviations: CTDI, CT dose index; MTF, modulation transfer function. Source: From Refs. 9,12.

An established and implemented quality control program is necessary to assess the performance of the CT unit and entails at least annual testing by a medical physicist and continuous quality control, typically conducted by an on-site radiological technologist. If diagnostic CT is to be performed on a PET/CT scanner, ACR accreditation can be obtained for CT imaging in addition to PET imaging. ACR accreditation is performed to formalize quality control further, and for CT, it was started in 2002, entailing the submission of data every three years. CT scanning protocols, clinical and phantom images, and dose measurements are included (5,6) in the accreditation. Clinical examples of studies performed at each scanner at the facility must use the appropriate protocol for each type of clinical examination performed by the facility. For example, for CT scanners used for pediatric patients an exam performed on a child between 0 and 5 years should be submitted (7). Clinical protocols need to be submitted accurately using the standard terminology to minimize confusion. Confusion is associated particularly with the number of data channels (N), the z-axis collimation (T), and the table speed per rotation (I) used in MDCT scanning. Information pertaining to specific scanners regarding these aspects is available on the accreditation portion of the ACR website (www.acr.org). Personnel requirements pertaining to physicians' supervision of CT examinations also exist under these guidelines. The remainder of the accreditation process utilizes the ACR accreditation phantom, which comprises four modules, each of standard 4-cm depth and 20-cm diameter containing water and tissue-equivalent material (Fig. 3) (5).

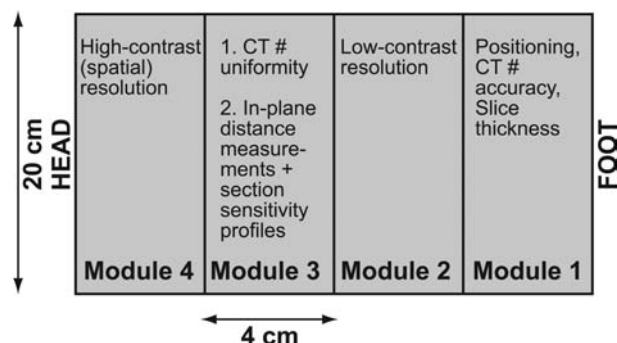


Figure 3 Schematic of the four modules of the phantom used for ACR CT accreditation. *Source:* From Figure 1a of Ref. 5.

Image Quality Control Procedures and Calibration

Alignment, CT Numbers, Scan Thickness

Scan plane alignment with the laser in the CT affords the assurance that patients can be positioned properly in the gantry by using the laser. Scan plane alignment is tested by centering a phantom using visual clues on the phantom surface, which will align the laser with radiopaque markers within the phantom. For ACR accreditation, imaging thickness must be 2 mm or less, and essential criteria satisfied in modules 1 and 4 of the phantom (5).

Accurate CT number calibration is key to providing an accurate attenuation correction for PET, let alone providing high quality clinical data on the CT. Consistency in the CT numbers reflects the constancy of the X-ray beam energy spectrum. For ACR accreditation, CT number calibration is tested on images of the phantom in module 1 by region of interest (ROI) analysis. Module 1 contains polyethylene, water, acrylic, bone, and air density materials. The mean and the standard deviation of the measured Hounsfield units are compared with the known densities of the materials that are within the phantom (Table 2). The CT number of water is additionally tested at each peak kilovoltage (kVp) setting that can be selected by an operator, regardless of the frequency of use in clinical practice. On a more practical, day-to-day basis, the Hounsfield unit measurement for water is tested daily.

Table 2 Acceptable Measurements in Hounsfield Units for Various Materials in the ACR CT Phantom

Material	HU
Polyethylene	−107 to −87
Water	−7 to +7 (±5 is preferred)
Acrylic	110 to 130
Bone	850 to 970
Air	−1005 to −970

Source: From Ref. 5.

More extensive testing is performed on an annual or semiannual basis.

The image slice width provides a measure of z-axis resolution and is related to the beam focal spot, detector size, and beam width collimation. In helical scanners, the couch speed and reconstruction algorithm are contributory factors. Evaluation of the image slice width is typically performed semiannually by the physicist. A piece of film is irradiated using milliampere-second (mA·s) at half the clinical level and the measured slice width is compared with the nominal thickness (5). Slice thickness for the ACR CT accreditation program entails measuring axial section widths and is also performed on module 1 of the phantom. The slice width in ACR CT accreditation should be within 1.5 mm of the designated width (5).

Low-Contrast Resolution

Increased image noise leads to suboptimal visualization of low-contrast subtle objects. Image noise depends on the amount of radiation that reaches and is processed by the detectors. Beam filtration and collimation, focal spot, and X-ray tube output affect the radiation output, while the sensitivity and calibration of the detector sensitivity play major roles in the reception of radiation information. The algorithm used for reconstructing the raw CT data affects the degree of image noise. Low-frequency algorithms decrease noise while spatial-resolution enhancing filters increase image noise (8).

Noise may vary up to 15%. Thus, baseline noise should be obtained by acquiring repeatedly (10 times) an axial image of the phantom and averaging attenuation values at the time of initial acceptance and calibration of the scanner. The daily standard deviation can then be tested against the baseline. If the standard deviation approaches 25%, the machine can be corrected on-site, although it is still considered usable (IPEM Report 77) (9). However, if the standard deviation varies by more than 50%, the scanner should be serviced before further use.

MDCTs are tested in the nonhelical mode for noise the same way as in a single-detector CT (SDCT) scanner, although multiple axial sections result from one acquisition, each of which are assessed for image noise. Not only must the standard deviation for the Hounsfield numbers be within an acceptable level for each axial section, but they must be similar across sections within the same multidetector acquisition, usually within 4–6%. This procedure is performed for the different MDCT detector configuration modes used. For helical imaging with MDCTs, individual slices need not be evaluated, but the phantom must be scanned in such a way as to ensure that the scan range includes a uniform portion of the phantom (5,10).

For ACR accreditation, module 2 in the phantom is used to measure low-contrast resolution with cylinders of 6 HU placed in background material. Abdomen and head CT protocols are assessed using standard window width and level settings. Regions of interest (ROI's) are placed over the smallest set of four low-contrast cylinders that can be clearly identified (5).

Uniformity

Uniformity testing assesses for a homogeneous image without artifacts. Uniformity is typically tested at all tube energies relevant to clinical practice on a phantom (11,12). Visual assessment confirms lack of artifacts, and ROI Hounsfield unit analysis at the image settings usually used for viewing clinical images is performed. ROI analysis entails comparing mean CT numbers for central and peripheral locations and comparing the differences between the values. Artifacts that may be identified include cupping (where the center will show lower CT numbers), bright, or dark, ring artifacts, and streaking. Any of these artifacts would lead to errors in the CT attenuation map for PET correction in addition to corrupting the CT image itself (11). For ACR accreditation, homogeneity or uniformity is measured using module 3 of the ACR phantom. The mean Hounsfield units of central and four peripheral positions are measured (5,9).

High-Contrast (Spatial) Resolution

Spatial resolution is the ability to identify differences in fine detail. Most often misalignment between the focal spot and the detectors or a deterioration of the focal spot is responsible for degradation of spatial resolution. Spatial resolution assessment typically entails the visual assessment of a repeating pattern. For quality control, spatial resolution can be assessed by scanning a bar pattern for subjective assessment. Objective evaluation entails imaging small or finite objects such as a point source, wire, or an edge of an object. In objective evaluation, the modulation transfer function over a repeating pattern of decreasing size can be measured as the standard deviation at each frequency and plotted over each spatial frequency (13). The spatial resolution may also be expressed as a point spread function or an edge spread function depending on the configuration of the phantom used for measurement. Since spatial resolution is unlikely to vary from one section to another, it is not necessary to test multiple slices in a multidetector scanner (9). A standard reconstruction algorithm should be applied to the images used to evaluate spatial resolution. While the usual reconstruction filters used in clinical studies may be used, reconstructions should also be performed with a filter that gives a high resolution to

maximize the sensitivity for any deterioration in spatial resolution.

Spatial resolution is assessed for ACR accreditation using module 4 of the ACR phantom. Imaging performed using abdomen and adult high-resolution chest protocols must be used with the correct reconstruction algorithm. The highest spatial frequency for which the bars and spaces are distinctly visualized is identified. At least a 5 line pair/cm bar pattern must be seen clearly for the adult abdominal protocol and 6 line pair/cm bar pattern for the high-resolution chest protocol (5).

Safety Quality Control: Dosimetry

The radiation dose from a CT scan is influenced by the beam energy or kVp, the tube current-time product, tube rotation speed, pitch, beam collimation, patient size, and any dose reduction modulation algorithms available in the scanner. As a method to measure radiation dose, the CTDI gives a measure of radiation exposure. CTDI, defined as the radiation dose normalized to beam width measured from 14 contiguous sections, requires the use of thermoluminescent dosimeters or film (14).

Therefore, for convenience, the $CTDI_{100}$ was developed to enable calculation of CTDI for 100 mm along the length of an entire pencil ionization chamber, regardless of nominal section width being used. $CTDI_{100}$ is expressed as the following: $f \times C \times E \times L/(NT)$, where f is the conversion factor from exposure to a dose in air, C the calibration factor for the electrometer, E the measured value of exposure in roentgens acquired from a single 360° rotation with beam profile of NT , L the length of the chamber, N the number of acquired sections per scan, and T the nominal width of each acquired section. $CTDI_{100}$, however, depends on position within the scan plane; therefore, the CTDI weighted ($CTDI_w$) provides a weighted average of the central and peripheral contributions to dose within an axial scan plane. $CTDI_w$ is as follows: $\frac{1}{3}CTDI_{100\text{center}} + \frac{2}{3}CTDI_{100\text{periphery}}$ (14).

To account for helical pitch or axial scan spacing the descriptor $CTDI_{vol}$ is the $CTDI_w$ multiplied by the number of data channels (N) times the nominal width of each acquired section (T) divided by the table feed per second (I) ($CTDI_w \times NT/I$) (14). This measure can be thought of as $CTDI_w$ divided by the pitch. The dose length product (DLP) is the product of the $CTDI_{vol}$ and the length of the scan in centimeters. This measure is used to estimate effective dose.

For quality control, the assessment of CTDI should be done at least annually, but initially more frequently until a stable baseline has been established (within $\pm 10\%$). If the value varies by 20% from baseline, service should be performed, and if it varies by 50% from baseline, the

scanner should be taken out of clinical use (9). The ACR protocol includes imaging of a 16-cm diameter phantom using an adult head acquisition, a pediatric abdominal acquisition, and an adult abdominal acquisition using protocols established at the clinical site (5). Direct axial measurements are utilized for CTDI measurements, although $CTDI_{vol}$ can be used as an estimate for spiral acquisition. A spreadsheet is provided so that CTDI, $CTDI_{vol}$, DLP, and effective dose from CTDI measurements can be recorded (5). Images from CTDI measurements are required to be submitted to verify that the appropriate phantom size and position, ion chamber usage, and correct parameters for CT acquisition are used.

Mechanical Quality Control

The gantry table should be tested with the equivalent of a patient's weight on the table. The distance the couch moves as measured by a ruler can be compared with the distance as calculated using the gantry display. Additionally, imaging can be performed of a phantom with two radiopaque markers separated by a known distance. A scout view is obtained to plan a helical acquisition that begins and ends at radiopaque markers. Visualization of the markers determines accurate calibration between the scanner and table. In PET/CT, the alignment between the CT and the PET gantry is tested daily to ensure that the anatomic coregistration is correct, both for attenuation correction and for CT to PET correlation.

PET/CT PROTOCOLS

The ability to optimize PET/CT necessitates an understanding of the capabilities of both technologies. Debate over the best approach for PET/CT protocol exists. The CT protocol, to some extent, is dictated by the need to use the acquired CT for attenuation correction. Generally, the quality of the CT images acquired in PET/CT may be less than that of diagnostic CT scans especially if the low-dose technique is used. The use of this technique is felt to be reasonable because a higher-dose diagnostic study may be subsequently required to further evaluate a finding, or because a recent diagnostic study might already have been performed. CT images are primarily acquired for attenuation correction, although they also are used to aid in lesion characterization and localization. A separate diagnostic study may be particularly important for the evaluation of small pulmonary nodules (15). Additionally, if administration of IV contrast is desired, a separate acquisition for this will avoid the technical problems that can occur when attenuation correction is performed using postcontrast studies.

CT Technique

Protocol decisions need to be made, some of which will balance the demands of the CT technique with the PET technique, for example, whether the thoracic and upper abdominal portion of the study is acquired in quiet breathing, mid-suspended breath hold, or expiration (16–18). Also, there may be a loss in CT image quality when a reduction in radiation dose is desired. Therefore, an understanding of the CT technique, the parameters affecting image quality, and dosage is helpful.

Oral Contrast

Opacification of bowel using oral contrast aids immensely in differentiating bowel from nodal or tumor masses and identifying bowel pathology. Up to a total of 1500 cc of dilute oral barium is administered during the prescanning phase to opacify small bowel. The amount of oral contrast utilized is graduated by patient weight (Table 3). Although dense barium may cause artifacts, the use of dilute CT oral contrast (usually 1.2% wt/vol or 1.3% vol/vol) results in very little perturbation of the attenuation correction matrix (19). A majority of the oral contrast is given prior to the administration of tracer, and then the last portion of this dose is administered 15 minutes prior to CT scanning. When patients are suspected of having gastric or upper abdominal pathology, the last dose of oral contrast is given immediately before the patient lies down on the scanning table in order to achieve better gastric distention.

In terms of the effect of oral contrast on PET imaging, Dizendorf et al. found an average variation in standardized uptake value (SUV) of 4.4% with about a 1.2% change in tumor SUV. The maximum overestimation of SUV in the clinical setting was 11.3% (20). Negative oral CT contrast has been proposed as an alternative to avoid this overestimation of PET activity (16) and works best in the setting of IV contrast, which improves contrast between the low attenuation bowel contents and enhancing surrounding structures.

Topogram

Once the patient is positioned on the table, a scout image or topogram is acquired so that the craniocaudal or

Table 3 Recommended Oral Contrast Administration

Patient weight	Volume (pre-tracer injection/ post-tracer injection)
<150 lbs	1.5 bottles/0.5 bottles
>150 lbs	2 bottles/1 bottle
Colostomy	Use half recommended dose

Table 4 PET/CT: Scan Extent and Positioning for Different Clinical Indications

	Area covered	Arm position
Brain	Head only (usually one bed position)	Arms down
Melanoma	Vertex to toes	Arms down
Cutaneous lymphoma	Vertex to toes	Arms down
Head and neck	Vertex to mid abdomen or thigh	Arms down
Thyroid cancer	Vertex to mid thigh	Arms down
Lymphoma	Vertex to mid thigh	Arms down
Solitary pulmonary nodule	Base of skull to mid thigh	Arms up
Lung cancer	Possible delayed chest (at 120 min)	Arms up
Metastatic disease GI, GU	Base of skull to mid thigh	Arms up

Abbreviations: GI, gastrointestinal; GU, genitourinary.

longitudinal distance to be covered during the CT and PET acquisitions can be determined. The field of view (FOV) at this time is displayed on the console to ensure that pertinent body parts are included in the scans.

Scans that begin at the base of the skull and terminate at the mid thigh are typically sufficient for evaluation of individuals with known or suspected lung, breast, gastrointestinal, and genitourinary tumors (Table 4). The orbits are not typically imaged in order to minimize radiation to the eye. However, the craniocaudal coverage is altered for specific clinical indications. For example, for head and neck cancers, image acquisition is initiated at the vertex of the head in order to ensure adequate visualization of the cervical lymph nodes and continues to the mid-abdomen or the mid-thigh level (21). For thyroid cancer, imaging is begun at the vertex of the head so that high cervical nodes can be assessed in their entirety and performed to at least the mid-thigh level and possibly more distally given the risk of distant osseous metastases. When assessing

patients with melanoma and cutaneous lymphoma, scanning starts at the vertex of the head and terminates at the toes.

CT Imaging

CT imaging is typically performed in a single helical continuous acquisition. Diagnostic thoracic and abdominal CT studies are usually acquired in sustained inspiration or expiration, respectively; however, a breath hold is not always utilized when acquiring a whole-body CT scan for attenuation correction for PET/CT. When used, a breath hold can be performed during the acquisition of CT images in the thorax and upper abdominal regions only (22). It requires careful education of both the technical staff and the patients. While this improves the quality of the lung CT images, the trade-off is a risk of misregistration artifact of the PET and CT images as well as attenuation correction errors that occur most frequently at the apices, the lung bases near the diaphragm, the anterior chest, and the upper abdomen (Fig. 4).

Traditionally, PET imaging without CT has been performed with the arms positioned adjacent to the thorax. With the advent of PET/CT, the arms are typically raised above the thorax for the acquisition of the PET images and CT. This positioning is advantageous for imaging the chest, but occasionally results in artifact that leads to difficulty when evaluating the neck. The body part of greatest interest therefore dictates the positioning of the arms.

IV Contrast

While the value of administration of IV contrast is well accepted in diagnostic CT, its role in PET/CT is still not established. The challenge is to obtain the ideal enhancement (e.g., arterial in the chest and portal venous in the abdomen) (16) of structures of interest on CT without encountering excessively high concentrations of contrast that might lead to beam hardening. Initial objections to IV contrast were related to beam hardening artifact in the attenuation-corrected PET images. There has been

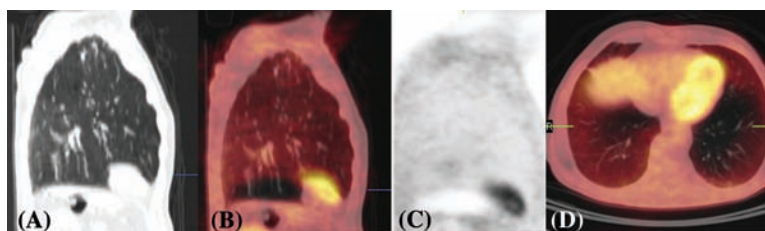


Figure 4 Misregistration artifact due to differences in position of the diaphragm between the CT acquisition and PET acquisition. Both studies were acquired during quiet breathing. (A) Sagittal CT scan of the chest, (B) sagittal fused PET/CT, and (C) sagittal attenuation corrected PET show the relative photopenia caused by under correction of the lung base. (D) The transaxial fused image shows the photopenic artifact.

Table 5 Intravenous Contrast Protocols According to Modality and Body Part

Body region	Volume	Rate	Delay
Brain CT	100 cc	Slow drip	Begin scan at end of infusion
Chest CT	100 cc	2–3 cc/sec ^a	30 sec ^b
Abdomen CT	1.5 cc/kg	3 cc/sec	80 sec
		2 cc/sec	90 sec
		1 cc/sec	100 sec
PET/CT	90–100 cc	1 cc/sec	70 sec

^aInjection rates about 4 cc/sec for aorta and pulmonary embolism assessment.

^bBolus tracking and automated triggering useful for aorta and pulmonary embolism assessment.

experimental data to suggest that the presence of contrast can lead to errors in correction of the PET SUV by up to 28% when contrast density approaches 200 HU (11). Similar clinical observations were made by Cohade et al., who found a limit of 239 HU to be the acceptable upper limit beyond which qualitative errors are detectable in attenuation correction (19). In general, most of the beam-hardening artifact occurs in the arm and subclavian regions on the side of IV contrast injection. Methods to minimize beam-hardening artifact have been studied and entail slower injection rates (1–2 cc/sec), slightly greater delays between injection and initiation of scanning (50–80 seconds), and a caudocranial scan direction (Table 5). In a study by Berthelson et al., a regular injection speed of 2.5 mL/sec with a 40-second delay from the start of the injection to the start of the scan has also been used without observation of visually appreciated artifact (23,24).

Maximizing CT Image Quality While Reducing Dose

A trade-off between image quality and radiation dose is always a consideration when scanning patients. Reducing the mA-s according to the size of the patient, decreasing the beam energy or photon fluence, or increasing the pitch on some scanners can reduce patient dose. Decreasing the dose however affects image quality, as the ratio of signal to noise related to scatter decreases. In general, MDCTs deliver a higher dose than single-detector counterparts (10).

Effect of Imaging Parameters and Patient Factors on Dose

Pitch

One acquisition parameter for helical CT that can be adjusted is the pitch, defined as the table translation or feed per 360° beam rotation (TF) divided by the total nominal width of the X-ray beam (W) in the z -axis. This

definition applies to both SDCT and MDCT (pitch = TF/W). The total nominal width can also be thought of as the product of the number of acquired axial sections per scan (N) and the width of each acquired section (T) (14). For single-detector helical CT technology, beam collimation is equivalent to reconstructed image section thickness, as the number of axial sections (or N) is 1 (Fig. 1). For example, a table movement of 10 mm while acquired in 10-mm sections is expressed as a pitch of 1. Before the development of MDCT, the pitch was previously defined as the table feed per 360° beam rotation divided by section thickness (TF/N). This definition is not used currently in MDCTs.

The radiation dose decreases with increasing pitch on SDCT (25). For MDCT, the z -axis beam collimation is wider than the reconstructed image section thickness. Radiation information from the X-ray beam is received by the detectors and segmented into typically thinner reconstructed sections (26,27) (Fig. 2). Unlike single-detector CT, many of the MDCTs are pitch independent in terms of radiation dose secondary to their use of a MDCT z -axis interpolation algorithm. With this technology, a change in pitch does not result in a change in dose to the patient (28). In this scenario, the pitch is no longer adjusted to minimize patient dose. An understanding of a specific scanner's MDCT technology, therefore, is necessary for understanding the relationship of imaging parameters to dosage. Changes in pitch for dose will affect image quality. With increasing pitch, artifacts are in general increased on single- and multidetector systems. Increasing the pitch on SDCT and some MDCT scanners decreases the scan time, minimizing the likelihood of image motion but increases the effective slice thickness. The effective slice width or the resultant section thickness is typically larger than the selected section width, secondary to the interpolation of helical data. The interpolation process is the estimation of a complete CT data set from the acquired helical measurement data. Some MDCT scanners have adaptive axial interpolation so that within a pitch range, the effective section width is independent of pitch.

Beam energy and photon fluence

Changing the energy of the X-ray beam alters the radiation dose to the patient. For example, McNitt-Gray notes that an increase from 120 kVp to 140 kVp resulted in a 39% increase in dose in an adult abdominal acquisition (14). Increasing photon fluence by adjusting tube current-time product (mA-s) raises the radiation dose linearly. A decrease in kVp will not decrease patient dose if photon fluence is increased to maintain image quality. For MDCTs in which dose is independent of pitch, the "effective" mA-s (mA-s/pitch) is selected by the operator rather than mA-s. The mA-s value is varied according to the pitch used so that the effective mA-s value is kept constant (14).

Collimation

For single-detector scanners, thinner collimation (i.e., image slice thickness) will result in higher radiation. The X-ray tube generates X-rays that are shaped by a prepatient collimator into a “dose profile” that is trapezoidal in the z-axis direction. At each end of the beam in the longitudinal direction, an area of the dose profile is unused and termed “wasted dose.” The wasted dose that occurs is removed from the image information by collimation after the radiation passes through the patient (post-patient collimation) or by detector self-collimation. Wasted dose occurs with each gantry rotation. The cumulative amount of wasted dose will be greater when using thinner collimation where more sections are obtained, as opposed to wider collimation and fewer sections for a given fixed length of imaging on a single detector scanner (14,29).

Thinner collimation on SDCT results in increased image noise and the tube current time may be augmented to compensate and decrease noise, thereby increasing patient exposure. With MDCTs, dose utilization is improved as the number of detector elements increase, given that fewer rotations and, therefore, less wasted dose is deposited for a given longitudinal distance of imaged tissue. However, for an MDCT, changing the beam collimation by selecting a detector configuration can influence effective dose. Typically, the dose increases with smaller detector configurations, for example 4×1.25 mm as compared with a larger configuration of 2×2.5 mm (14).

Patient size

For a fixed set of CT parameters, the dose will increase as patient size decreases. In small patients, there is less tissue and therefore less attenuation of the radiation as it passes through the patient, leading to larger doses. In contrast, when a larger patient is imaged, the exit radiation is less intense than at its entrance, with higher radiation doses at the skin surface, leading to smaller overall doses.

Applying adult techniques for scanning smaller patients may lead to excess radiation exposure without an improvement in image quality. Therefore, strict attention to dose is necessary, particularly when dealing with the pediatric population. Given the smaller body size, high-quality images can be obtained using size- and weight-based imaging protocols (Table 6). When performing PET/CT of pediatric patients, the imager must appropriately reduce the preset parameters. Recently, reduced-dose CT (80 kVp, 5 mA·s, 1.5:1 pitch) in pediatric anthropomorphic phantoms has shown good-quality attenuation correction for PET/CT (30).

Dose modulation

Currently, most manufacturers provide anatomic tube current modulation algorithms for clinical practice. The output of the tube is adjusted to account for differences in patient geometry (2,29,31,32). Tube current modulations methods can

Table 6 Pediatric Protocol for PET/CT with IV Contrast

Parameters	
CT acquisition	• Topogram 50 mA·s, 120 kV • Detector: 0.625 • Recon 5 mm/5 mm • mA: 5 mA·s or with dose modulation, 95 mA·s • kV: 80–110 • Scan FOV: 700 mm • Reconstruction: Soft tissue and lung kernel
	Injection of IV contrast:
	• Volume: 2cc/kg • Rate: 2 cc/sec • Delay 70 sec
Dose of FDG:	• 0.22 mCi/kg for oncology • 0.29 mCi/kg for melanoma • Maximum dose 15 mCi with weights >114 kg or 250 lbs • Minimum dose 5mCi with weights <23 kg or 51 lbs

Abbreviation: FOV, field of view.

Source: From Refs. 27,30.

obtain necessary information from a topogram or utilize the information during image acquisition. Tube current modulation can be within the axial xy plane, termed angular modulation, or in the z-axis, termed longitudinal modulation. Angular tube current modulation entails selection of an effective target tube current–time product, and while the tube current–time product within an axial section will fluctuate, the effective mA·s for each section will be overall constant. For example, in the shoulder region, the mA·s may be increased when the beam passes through both shoulders, as opposed to the anteroposterior dimension, in which the beam passes through less attenuation structures and can be decreased (Fig. 5). Longitudinal tube current modulation in the z-axis takes into account the relative differences in the thickness between, for example, the neck and abdomen (14,31) (Fig. 6). Depending on the manufacturer, a reference factor, such as a reference effective mA·s, reference noise index, reference image acquisition, or reference standard deviation or image quality level (manufacturer dependent), is selected, and the tube current time varied in the x, y, and z dimensions so that image quality matches the desired level (31). In the future, automatic exposure control that adjusts the overall tube current according to patient size will help prevent over or under irradiation.

Dose-Related Considerations Pertaining to Attenuation Correction CT

Although occasionally two scout images may be acquired in diagnostic, cardiac, craniofacial, and mandible CT, in

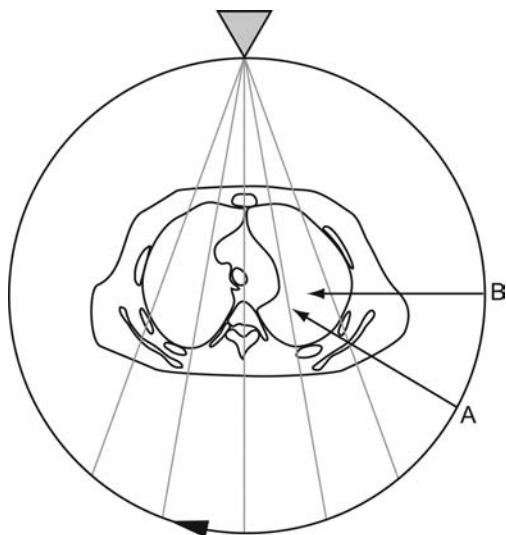


Figure 5 Angular anatomic tube current modulation. Diagram demonstrating principle of tube current modulation in the axial plane termed angular modulation. The tube current is adjusted as the X-ray source rotates in a 360° path around the patient. When the X-ray source is positioned at a point at which the beam would pass through areas of the body that attenuate (*point A*) to a greater degree, as in this example, the scapula, the tube current times are higher in comparison to a position in which irradiation of less attenuating tissues would occur (*point B*).

most diagnostic CT acquisitions and in PET/CT, usually only an anterior topogram is obtained to provide information concerning the thickness of the body. Typically, for the acquisition of the CT for attenuation correction kVp is set at 120 to 140 kV and held constant through the entire body acquisition and dose modulation is suggested to minimize radiation exposure.

Absorbed radiation dose has been estimated for PET imaging in combination with either a low-dose or diagnostic quality CT scan and for a PET study performed alone. Including the topogram, the effective radiation dose for all acquisitions involved in a PET/CT has been reported to range from 8.5 to 26.4 mSv, depending on the quality of the CT scan (33). A topogram contributes a very small amount to the radiation dose, on the order of 0.2 mSv. The PET portion based on 10 mCi or 370 MBq delivers 7 mSv. A low-dose CT technique is associated with effective doses of 1.3–4.5 mSv, while a diagnostic quality CT with contrast delivers between 14 and 18 mSv (33).

Improving CT Image Quality

The variables that can be controlled during CT image acquisition and reconstruction to enhance imaging quality also affect patient dose. Therefore, a trade-off between image quality and patient dose occurs. Image noise, spatial,

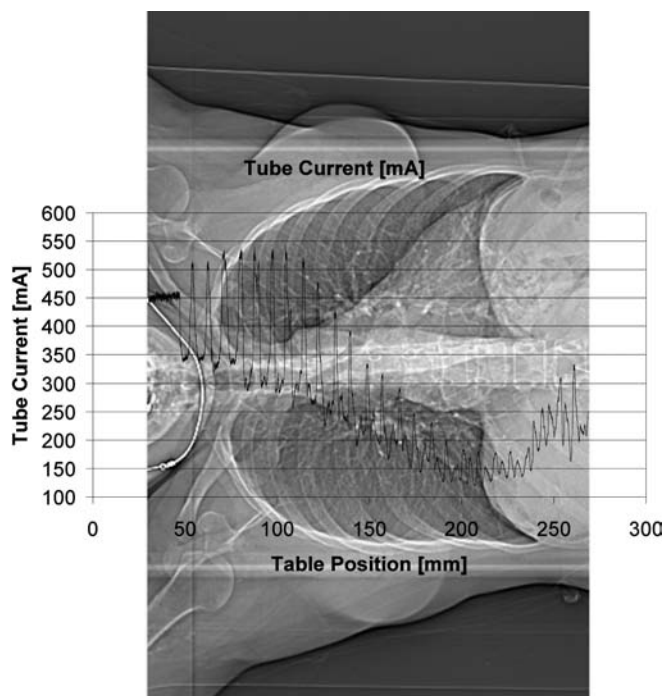


Figure 6 Angular and longitudinal anatomic tube current modulation. Scout topogram demonstrating thoracic structures with superimposed corresponding tube current in mA utilized for the imaging at different points in the thorax. The average mA used in the shoulder region is higher than that used for imaging the mid and lower thorax. More distally in the upper abdominal region, an upslope in the average mA-s occurs secondary to the increased soft tissue density of the upper abdominal organs as compared to the lower thorax, which comprises a great degree of by lung. The difference between the peaks and troughs of the mA-s in the shoulder region reflect the angular tube current modulation in the *xy* plane. This difference becomes smaller as imaging progresses caudally where the attenuation and thickness of the tissues irradiated do not differ to as great degree in the *xy* plane. *Source:* Courtesy of Siemens Medical Solutions Malvern, PA.

and temporal resolution are factors that affect image quality. This makes multiple reconstructions of image data with different parameters in order to enhance assessment of varying structures of interest useful (Table 7).

Image noise is affected by the radiation dose and, in turn, parameters that affect the radiation dose, such as lower beam energy, lower mA-s, and smaller collimation. Image noise affects differentiation of low-contrast (typically soft tissue) objects to a greater degree than high-contrast objects (e.g. lung). Soft-tissue structures that have small differences in density are difficult to evaluate in the presence of high image noise (27). Reconstruction of data into thicker sections with low-frequency reconstruction algorithms and application of post-reconstruction filters

Table 7 PET CT Protocol: CT Reconstructions^a

	CT			
	Mode	Reconstruction thickness/ increment (mm)	Reconstruction algorithm	Reconstruction FOV (cm)
Head	Helical	5 q. 5	Bone and subdural	25
Abdomen/pelvis/chest	Helical	5 q. 5	Soft tissue	70
				50 ^b
Lungs	Helical	5 q. 5	High frequency (for lung)	Smallest FOV to contain lungs (35–40)
Extremities	Helical	5 q. 5	Soft tissue	70/50

^aFor better characterization of an osseous lesion, directed high frequency algorithm reconstructions can be performed.

- kVp is generally held constant throughout the entire acquisition with 120–140 kVp being typical in adults.
- A single target mA-s is set for the entire attenuation correction CT acquisition, however, mA-s may vary if dose modulation software is used in the acquisition.

^bA second reconstruction can be performed using a 50-cm FOV for the entire body. This will yield a slightly improved CT image.

Abbreviation: FOV, field of view.

will improve soft-tissue evaluation and enable better attenuation measurements, although at the sacrifice of spatial resolution (Fig. 7).

Spatial resolution is the ability to resolve small structures and is improved on the z-axis by thinner beam collimation, the spiral interpolation process that determines the effective section width, and smaller detector configurations or “section collimation” in MDCT (34). As mentioned, the effective section width is often larger than the selected section width. The effective section width is pitch dependent for SDCTs and MDCTs that utilize a 360° or 180° spiral interpolation approach (29). A z-filter MDCT adaptive axial interpolation has been developed that does not utilize the 360° or 180° interpolation so that

the increasing pitch within a range of 0.5 to 2.0 is not associated with wider effective section widths. With this pitch-independent technology, image noise may be increased when higher pitches are utilized, and therefore MDCTs with z-filter reconstruction have automatic adaptation of tube current so that an “effective” mA-s and degree of image noise can be maintained (29).

Spatial resolution can be improved by the selection of appropriate postacquisition parameters such as the FOV, reconstruction algorithm, and section thickness. Smaller pixel sizes and therefore smaller fields of view are beneficial. Given that the FOV is encoded into a 512 × 512 matrix, pixel size in the x or y dimension is determined by the FOV divided by 512. Therefore the FOV should be

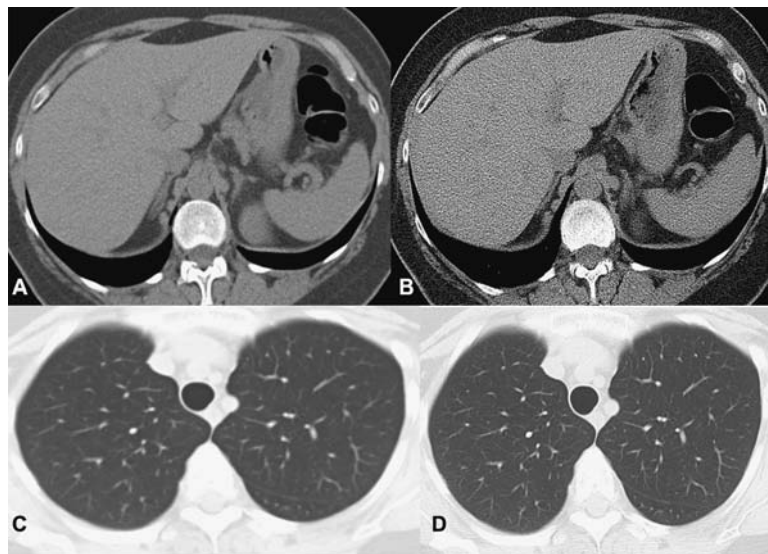


Figure 7 Effect of reconstruction algorithm on image quality. Image from a PET/CT of the liver reconstructed using (A) low-frequency algorithm has less image noise than the same image produced with (B) a high-frequency reconstruction algorithm. The lower spatial resolution associated with (C) a low-frequency reconstruction algorithm, however, is best demonstrated in the lungs, in comparison to the same section reconstructed using (D) a high-frequency algorithm.

reconstructed to include all necessary body parts yet be small enough so that pixel size is kept to a minimum and spatial resolution maximized. An FOV of 35 to 50 cm is typically used in diagnostic CT and adjusted according to a patient's size for the thorax and abdomen. The CT portion of the PET/CT is frequently reconstructed using a large FOV (70 cm) for assessment of the soft tissues (Table 7). A second reconstruction of the CT data using 50 cm provides some improvement in spatial resolution even for soft tissues for the torso. While the CT is acquired for attenuation correction purposes with as large an FOV as allowed, typically 70 cm, the CT can then be separately reconstructed with these smaller diameter FOVs. For better evaluation of the lung parenchyma, data can be processed at smaller FOVs to improve spatial resolution on the order of 35 to 40 cm (Fig. 7). A high-frequency reconstruction technique increases spatial resolution at the expense of image noise and is most useful for assessment of the lung and for osseous structures. (Fig. 7). Therefore, given the rapidity of image reconstruction using current CT technology, raw data can be processed using both high- and low-frequency algorithms to maximize assessment of soft tissue, lung, and bone optimally.

The use of thinner sections reduces partial volume effect, although it also results in an increase in the number of images that need to be reviewed. MDCT scanners provide greater flexibility in terms of section thickness, as thick or thin sections can be obtained from the same helical study. For a majority of MDCTs, slice thickness on the order of 1 mm can be obtained if using a smaller beam collimation and detector configuration. The use of thinner collimation, however, is typically associated with increases in radiation exposure secondary to wasted dose and increases in X-ray tube current to maintain image quality. The capabilities of each scanner can be assessed by review of manufacturer information. When assessing internal characteristics and morphology of a small lesion such as a lung nodule targeted FOVs and thin sections are helpful and can be retrospectively reconstructed from raw data if desired (27).

Temporal resolution is influenced by the speed of image acquisition. Low temporal resolution leads to a longer scan duration, which increases the probability of motion artifacts. For thoracic and abdominal studies, when suspended respiration is performed, shorter breath hold requirements, i.e., faster acquisitions, minimize misregistration artifact from breathing. Misregistration artifact on CT alone occurs when lesions, particularly small ones, may not be imaged because of motion out of the imaging plane during acquisition. Temporal resolution increases with shorter scan times, also termed the rotation time or the time for the gantry to rotate 360°, and a larger number of MDCT detector rows. Shorter scan times are very important for the imaging of small structures affected by cardiac motion.

Scan times are currently on the order of 0.3 to 0.5 s per rotation. Multiple detector rows enable more rapid imaging of a specified longitudinal distance or permits imaging of larger distances without increasing image time.

Multiplanar Viewing of PET/CT Data

Software packages enable the interpreter to interactively view attenuation-corrected PET, non-attenuation-corrected PET, CT, and fused PET/CT data in multiple orthogonal planes. Near isotropic reconstruction of CT information and the continuous nature of PET data enable postprocessing techniques. CT data are typically displayed in multiple orthogonal planes as multiplanar reconstructions (MPRs). MPRs are two-dimensional slabs reconstructed at selected intervals through a volume of data (35,36). The displayed image reflects an average of the attenuation of voxels along each array within the slab, and the volume of CT data can be viewed on any selected plane. Maximum-intensity projections (MIPs) are similar to MPRs except the maximum instead of the average voxel value is utilized for image reconstruction (35,36). MIPs are typically used for three-dimensional display of PET data. Multiplanar viewing tools are integrated within PET/CT viewing software to improve lesion characterization. For example, discrimination of nodules from mimickers such as vascular structures or parenchymal scars on CT is facilitated. Newer versions of PET/CT software incorporate fly through and three-dimensional renderings of CT and/or PET as well (Fig. 8).

Protocol Considerations According to Body Part

Diagnostic CT acquisition protocols differ from PET/CT for a number of reasons. In part, current state of the art

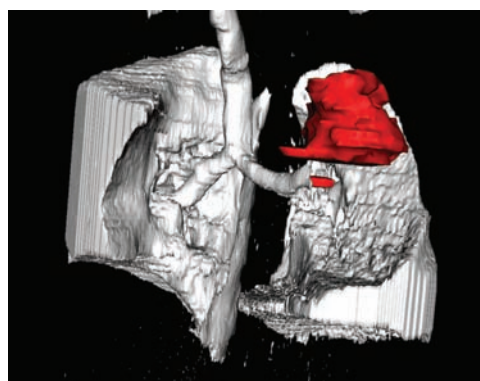


Figure 8 Three-dimensional rendering of FDG PET uptake in a lung cancer superimposed on the 3D rendering of the lungs and airways. This image provides a different means of evaluating the cancer's relationship to airways and the normal lung. *Source:* Courtesy of Kent P. Friedman, MD.

Table 8A Diagnostic Head CT Acquisition Protocol

CT type	Mode	kVp	mA·s	Detector collimation (mm)	Slice thickness (mm)	Table feed/rotation (mm)
16-slice dedicated diagnostic MDCT (Siemens Sensation) ^a	Sequential	120	200	0.75	4.5	9
6-slice PET/MDCT (Siemens Biograph) ^b	Helical	130	240	3.0 ^c	4	15

^aDiagnostic quality.^bPET/CT.^cFor diagnostic studies collimation as small as 0.5 mm is possible. This reconstructs to 0.63-mm slice thickness.**Table 8B** Head CT Image Reconstruction

Application	Section thickness (mm)	Recon increment (mm)	Recon kernel	FOV (mm)
Dedicated diagnostic study ^a				
Brain	4.5	4.5	H45	250
Subdural	4.5	4.5	H40	250
Bone	4.5	4.5	H70	250
PET/CT (6-slice) ^b	4	2.5	H10 VS or H45 medium	300

^aDiagnostic quality^bPET/CT

PET/CT scanners do not permit changing of acquisition parameters within a continuous skull to thigh study. The radiologist or nuclear medicine physician should be cognizant of differences between diagnostic CT and PET/CT in terms of acquisition and reconstructions. The detailed discussion of diagnostic CT protocols for clinical indications and body parts is beyond the scope of this chapter, but sample protocols are provided for comparison with the PET/CT protocol (Tables 8–10). Nonetheless, certain consideration should be given to tailoring protocols to optimize imaging of certain regions.

For improved analysis of the lung parenchyma on CT, the raw data of the thorax can also be reconstructed to

maximize spatial resolution utilizing a smaller FOV to include the lungs but exclude the soft tissues of the thorax (Fig. 9). The FOV is typically on the order of 30 to 35 cm, using a high-frequency reconstruction algorithm. Section thickness on the order of 5 mm is sufficient for assessment of the lungs and soft tissue. Similarly, in the brain, a smaller FOV, usually 25 cm, may be used to reconstruct the CT with filters that optimize visualization of brain and bone.

Postprocessing review of the PET/CT should be performed to assess for misregistration, especially in the head, where slight movement can cause significant artifact in the attenuation correction and artifactual asymmetry (Fig. 10). Patient motion that occurs between the CT acquisition and the PET acquisition should be briefly assessed, and if there is abnormality in areas of misregistration, repeat CT and PET acquisitions of problematic areas need to be performed. In the pelvis, changes in bladder distention between the two acquisitions can lead to misregistration of pelvic organs and ureteral urinary activity may at times be problematic even with PET/CT

CT Artifacts

An artifact that can be encountered in spiral CT is the “spiral” artifact, which can occur with SDCT and MDCT and occurs secondary to the spiral interpolation process.

Table 9A Sample Dedicated Chest CT Acquisition Protocols

CT type	Detector configuration	kVp	mA·s ^a	Rotation time (sec)	Table feed mm/rotation ^b
Single-detector Helical	7 mm	140	120	0.75	Pitch 1.5
4-slice adaptive array (Philips, Siemens)	4 × 1.0	140	120	0.5	8–12
4-slice Matrix array (GE Lightspeed)	4 × 2.5	140	120	0.75	15
6-slice PET/CT ^c (Siemens Biograph)	6 × 0.625	130	95	0.6	15
16-slice (Siemens Sensation)	16 × 0.75	120	160	0.4	14
16-slice (Toshiba)	16 × 1	120	150	0.5	16
64-slice (Siemens Sensation)	32 × 0.6	120	160	0.33	Pitch <1

^aFor nodule confirmation or follow up, reduced dose technique on the order of 60 to 100 mA·s can be utilized.^bPitch is typically on the order of 1 to 2.^cAdditional delayed imaging for a pulmonary nodule assessment at 2–3 hours after injection.

Table 9B Chest CT reconstructions, Diagnostic CT

	Soft tissue	Lung
Filter	Low frequency (standard, b40)	High frequency (bone, b60)
Slices	5 q. 5 mm	5 q. 5 mm 1 q. 10 mm (High resolution sections)
FOV	35–450 mm Wider FOV for melanoma, breast, and lymphoma to include axilla	Tailored to exclude soft tissues and include lung parenchyma (350–400 mm)

Abbreviation: FOV, field of view.

High- or low-density artifacts can surround high-contrast objects that are inhomogeneous in the z-axis and rotate through longitudinal plane, such as ribs. Increasing the pitch increases these artifacts (29). Similar to spiral artifacts, cone-beam artifacts are encountered in CT scans of high-contrast objects, including bones and orthopedic hardware and occur particularly with MDCT. The MDCT X-ray beam has a wide fan shape in the z-axis (Fig. 2), and therefore all the rays of the X-ray beam do not pass through the patient in a perpendicular fashion but rather a “cone angle.” The cone angle is the greatest at the ends of the detector array. The cone angle increases with the number of detector rows, if the detector rows’ thickness in the z-axis is kept constant. When the cone angle is not accounted for, cone-beam artifacts occur. For four-MDCTs, cone beam artifact is tolerable without correction. Decreasing pitch or table feed and narrower detector element configuration can reduce cone-beam artifacts (25). MDCTs with 16 or greater detector rows have algorithms that account from cone-beam geometry (29).

Beam-hardening artifacts occur when high-density material such as hardware alters the spectral characteristics of the radiation beam, leading to streak artifact of low and high attenuation in the surrounding area. Increasing the kVp and mA-s may improve image quality but lead

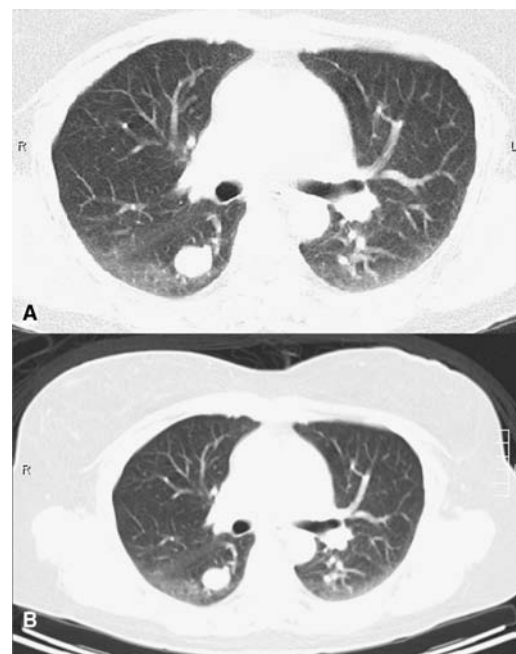


Figure 9 Smaller FOV utilized for reconstruction of (A) CT data that is obtained for attenuation correction decreases pixel size and improves spatial resolution, improving assessment of the lung parenchyma. A high frequency reconstruction algorithm was also utilized. In distinction, (B) the data reconstructed with a large FOV and soft tissue (low-frequency) reconstruction algorithm enables assessment of the soft tissues along the chest wall for CT and PET evaluation but provides, as viewed in lung window setting, lower resolution secondary to the larger pixel size related to the larger FOV and blurring related to the reconstruction algorithm. Abbreviation: FOV, field of view.

to an increase in patient dose. In practice, in PET/CT, the CT acquisition parameters are not altered sufficiently to eliminate the artifact. Not only can artifact obscure anatomic detail at the level of the hardware (Fig. 11), but it can also cause errors in the attenuation matrix and the corrected-FDG PET image at that level.

Table 10 Sample Diagnostic Abdomen CT Acquisitions

CT type	Detector configuration	Rotation time	kVp	mA-s	mm/rotation	FOV (mm)	Slice thickness per reconstruction interval
16-slice dedicated diagnostic MDCT (Siemens Sensation)	16 × 0.75	0.4	120	180	14	Tailored ^a	4 mm per 4 mm interval
6-slice PET/MDCT (Siemens Biograph)	6 × 0.625	0.6	130	95	15	700 for routine PET/CT ^b	5 mm per 5 mm interval

^aFOV is tailored to the size of the patients depending on abdominal girth.

^bReconstruct again at 500 mm with medium filter for improved resolution.

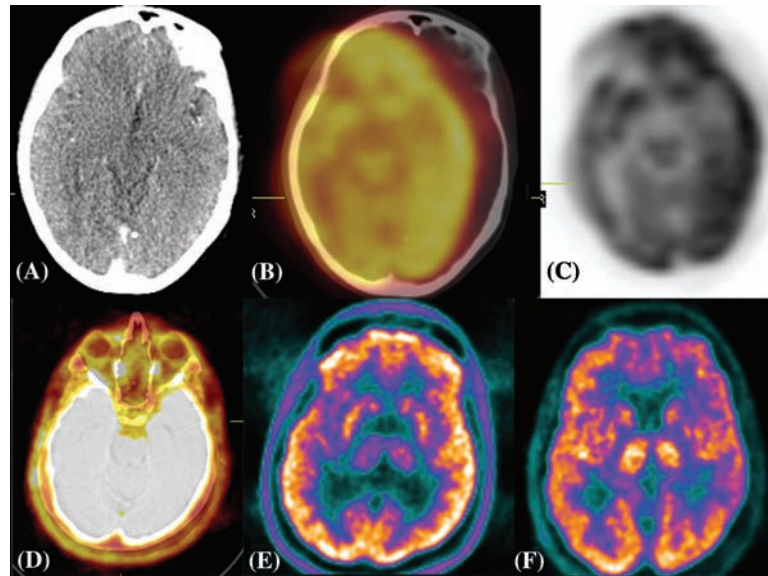


Figure 10 Images obtained in a patient with dementia (A–C) show (A) the CT and (B) the PET superimposed on the CT. Examination of (C) the attenuation corrected PET shows spuriously asymmetrical uptake between the right and left cerebral cortices. In a second patient very subtle misregistration is seen in (D) as the lower PET slice superimposed on the CT. The mild asymmetry seen in the uncorrected image (E) (*left > right*) appears erroneously reversed in the resulting attenuation-corrected image (F), where *right > left* uptake is seen.

SUMMARY

An understanding of issues of quality control and safety surrounding performance of CT will ensure optimal quality CT and patient safety while containing the radiation-absorbed dose to the patient. Understanding of some of the parameters measured in quality control procedures and calibration will help the practitioner troubleshoot problems. Parameters, which affect qualitative and quantitative image quality on CT, include alignment, calibration of Hounsfield unit numbers, the consistency of section thickness, the ability of the scanner to resolve low-contrast objects, the uniformity across the imaging field, and the spatial resolution of the scanner. Radiation dose to the patient is of primary concern in operating CT scanners. Thus, routine quality control procedures require that the tube current be predictable and accurate. Finally, the position of the table in relation to the lasers needs to be calibrated and in the case of PET/CT precisely aligned with the PET scanner for developing the attenuation correction matrix and image registration.

The CT protocols used routinely for diagnostic imaging can be finely tuned for a particular body part, clinical question, e.g., pulmonary embolism, or even more precisely for a small object such as a pulmonary nodule. Oral and IV contrasts can be used, as appropriate, to improve the quality of the information from the CT images. Always, the tailoring of the CT acquisition parameters should be performed with the radiation-absorbed dose in mind. The pitch, beam energy, and collimation should also be tailored. Reduction of the tube current for smaller patients, especially children and adolescents, is critical.

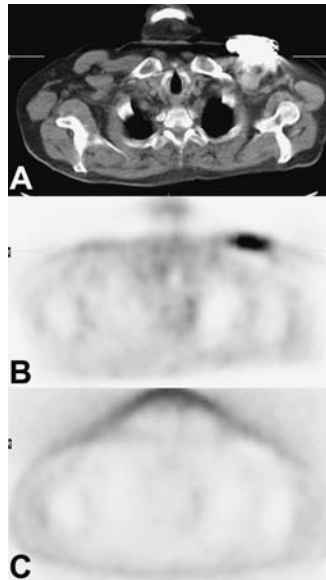


Figure 11 (A) Transaxial CT image through the chest shows the density as well as the beam hardening artifact caused by a pacemaker implanted in the left chest wall. On the corresponding attenuation-corrected (B) PET image there is artifactually increased uptake seen at the site of the pacemaker. However, when the corresponding transaxial slice from (C) the uncorrected PET image set is examined, there is no increased uptake seen. This increased uptake (B) is caused by overcorrection at the site of the high-density object. In addition there is undercorrection just deep to the site of the pacemaker.

Dose-modulation software has become a major tool in balancing the image quality with patient dose.

Viewing software for PET/CT should permit the reader to take advantage of all the information available in the CT, e.g., different windows for bone, soft tissue, and lung, and provide both the registered PET and CT data in at least three orthogonal planes with more flexibility along the plane of reconstruction if possible. Finally, the uncorrected PET images should always be available for comparison. For CT performed for attenuation correction, CT acquisition protocols are more constrained, for example, requiring reconstruction with a constant FOV across the entire acquisition. For inspection of the CT information, reconstruction of data should be optimized whenever possible for the particular ROI. Postprocessing by restricting the FOV for reconstruction, different filters, and appropriate window settings can all help with this.

An awareness of CT-related artifacts such as cone beam, beam hardening, and respiratory motion will help the practitioner understand the problems in CT images. Such artifacts on the attenuation correction matrix and therefore the corrected PET images can be identified by inspection of the uncorrected PET images in addition to the CT data.

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2

PET Instrumentation and Methodology

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INTRODUCTION

Positron emission tomography (PET) has emerged as a powerful imaging modality with applications in a number of fields including oncology, cardiology, and neurology. Advances in both radiopharmaceutical chemistry and instrumentation, combined with extensive validation in a range of disease settings, have led to widespread acceptance of its clinical application. This has been particularly evident in oncology where combined PET and X-ray computed tomography (CT) scanners (Fig. 1) (1) are extensively used in conjunction with the glucose analog ^{18}F fluoro-2-deoxy-D-glucose (FDG). The foundations of PET are based upon a convergence of two independent factors. The first factor is related to the chemistry of positron-emitting radionuclides, and the second to the physics of their radioactive decay.

Positron-emitting isotopes exist for a number of elements that are found in organic molecules in the body. Carbon, nitrogen, and oxygen all have isotopes that decay by positron emission (^{11}C , ^{13}N , ^{15}O), and these can be substituted directly into biomolecules of interest with very little effect on the molecule's behavior. The half-lives of these isotopes are of the order of only a few minutes, making them suitable for administration to patients. ^{11}C , ^{13}N , and ^{15}O have half-lives of 20, 10, and 2 minutes, respectively, which means that patients do not receive

high radiation exposure for extended periods after the imaging procedure is complete. Radio-labeled material can be used in vivo to study a range of biological processes including, for example, tissue perfusion with ^{15}O -labeled water. In addition to natural substrates, analogs such as FDG can be labeled with positron emitters. ^{18}F -labeled FDG is a glucose analogue that has the advantage that phosphorylated FDG in cells cannot be further metabolized and is effectively trapped, allowing its distribution in the body to be conveniently measured with PET. It also has a relatively long half-life of 110 minutes, which means that it is practical to use and particularly well suited to clinical application. FDG is by far the most popular tracer used for current clinical applications, primarily because it can exploit the fact that malignant tumors tend to exhibit elevated glucose metabolism compared with normal tissue. However, a major strength of PET is the potential for the development of new tracers that will satisfy evolving clinical needs and research interests. Increasingly, new radiotracers labeled with ^{18}F are being developed with the potential for more widespread distribution than the shorter-lived positron emitters.

In addition to their favorable chemical properties, positron-emitting isotopes have a characteristic mode of radioactive decay that lends itself to accurate measurement. Shortly after their emission, positrons *annihilate*

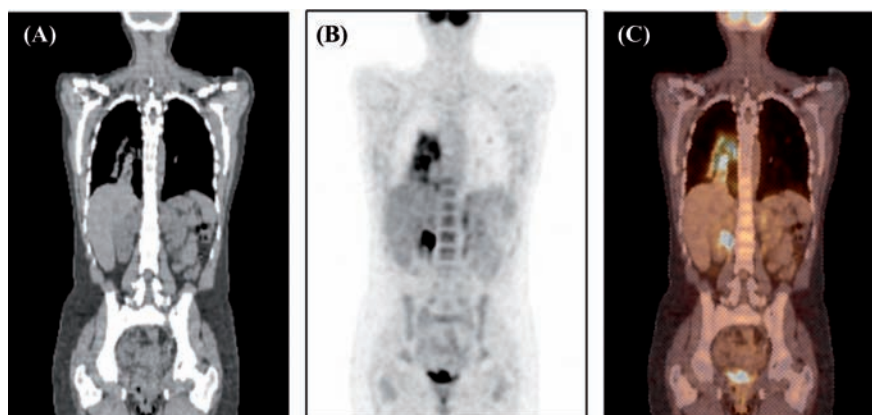


Figure 1 Combined PET/CT scanners allow convenient acquisition of spatially aligned images under the assumption that the patient did not move between the two sequentially acquired scans. Coronal CT (A) (gray scale) and PET (B) (inverse gray scale) images are shown, along with a fused representation (C) (CT in gray scale, PET in color overlay).

with electrons in the body producing two 511-keV gamma photons that are emitted almost exactly 180° apart. Measurement of these photons using detectors that not only record their positions but also the time of their measurement allows for a mode of acquisition referred to as *coincidence detection*. Coincidence detection obviates the need for the physical collimation that is required in single-photon gamma camera imaging and results in increased sensitivity and improved spatial resolution. Unlike in gamma camera imaging, where resolution is strongly dependent upon the distance between the source and the camera, the high spatial resolution that can be achieved with PET is much more uniform over the field of view. An additional advantage of detecting back-to-back annihilation photons, as opposed to single photons, is the potential for accurate attenuation correction using anatomical information from, for example, a sequentially acquired CT. The combination of accurate attenuation correction and relatively high spatial resolution and sensitivity mean that PET images accurately reflect the local concentration of the radioactive tracer within the body. This property means that PET can be used to quantify physiological and biochemical processes in absolute terms, e.g., tissue perfusion in mL/min/g or glucose metabolism in mol/min/g.

In this chapter we focus on the imaging devices that have been developed to exploit these favorable chemical and physical properties. The basic principles of PET image formation, and the design principles behind modern scanners will be reviewed. PET instrumentation continues to undergo rapid evolution, and we will discuss trends in scanner design. Throughout the chapter we will emphasize the implications of methodological issues on image quality and the technical pitfalls to be avoided.

POSITRON EMISSION AND ANNIHILATION COINCIDENCE DETECTION

PET measures the distribution of positron-emitting radiopharmaceuticals within the body by detecting the gamma photons that are produced shortly after positron decay (Fig. 2). Positrons are short-lived particles that have the same mass as electrons but opposite charge. They are created during the decay of unstable, proton-rich isotopes, and the process involves the transformation of a proton within the nucleus to a neutron. As a result of this transformation, positrons (β^+ particles) are emitted from the nucleus with a range of energies. This range has a specific distribution with a maximum value that is characteristic of the parent isotope. After emission, the positron propagates through the surrounding material (the patient's body in the case of clinical imaging), losing energy as it collides with different electrons, and finally comes to rest a short distance from its point of emission. The distance traveled by the positron is a function of its energy and is relevant because it places a limit on the spatial resolution that can be realized in the resulting images. ^{18}F produces relatively low-energy positrons with an average range of only 0.3 mm, whereas the average range of positrons emitted from ^{82}Rb is 2.6 mm. Once a positron has lost most of its kinetic energy, a collision with an electron may result in an electron-positron annihilation. Both particles are destroyed, and conservation of energy ensures that their rest masses are converted into two 511-keV gamma photons. Conservation of momentum, which is close to zero at the time of annihilation, means that these gamma photons are emitted approximately 180° apart. By surrounding the patient with detectors, the 511-keV photons that result from electron-positron annihilation can be recorded, but when considered

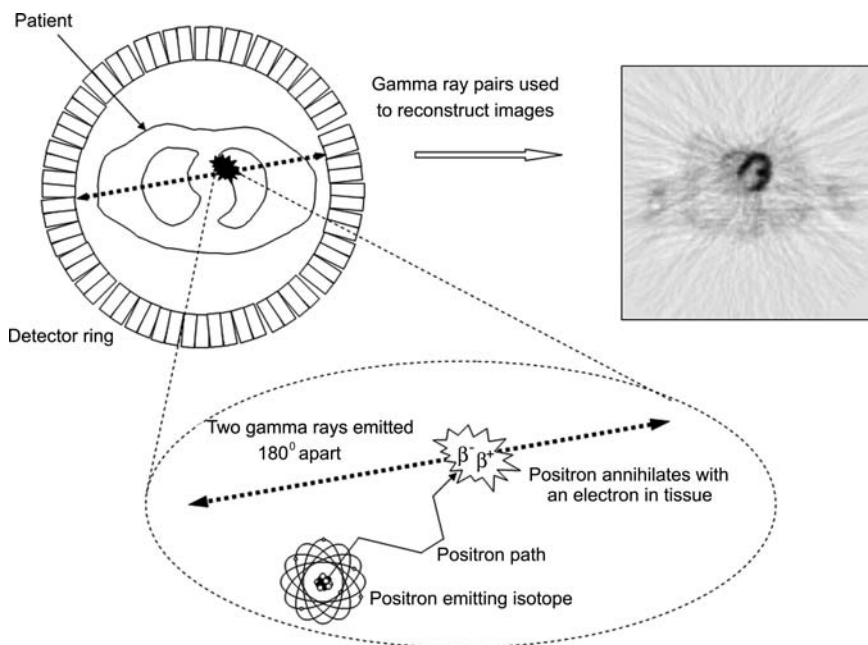


Figure 2 Positron emission gives rise to two 511-keV photons that are emitted simultaneously in opposite directions. Back-to-back photons of this sort can be detected in a coincidence mode that allows simultaneous acquisition of multiple projections. These projections can then be used to reconstruct images of the radioactivity distribution using the theory of computed tomography.

individually, each photon provides little information about the distribution of the positron-emitting source. This is because, in the absence of any physical collimation, a single photon recorded by the detectors could have originated from anywhere within the field of view. To overcome this problem, PET scanners operate in a *coincidence* mode that takes advantage of the fact that annihilation photons are emitted, not just in pairs, but in pairs that are emitted simultaneously.

From the numerous single photons that are recorded by a PET scanner, coincidence detection involves the association of pairs of photons that were detected within a short period of time. This time period (of the order of 10 nanoseconds) is called the coincidence time window and is a property of a particular scanner. Pairs of photons that were detected within this time window are assumed to have originated from the same annihilation event, and their measurement is called a coincidence event. Because annihilation photons are known to be emitted 180° apart, it can be assumed that the location of the electron-positron annihilation lies somewhere along the line joining the points where the two photons were detected. In practice there will be a small angular deviation (noncolinearity) from the expected back-to-back photon emissions as the positron and electron may have some residual momentum at the time that the annihilation occurs. Assuming all annihilation events occur along a straight line joining corresponding detection sites is therefore not strictly correct and contributes to

a loss of spatial resolution. In general, coincidence detection does not provide information about the location along the line where the annihilation took place. However, by recording many thousands of coincidence events over the course of a scan, a projection of the activity distribution can be estimated. If projections of this sort are measured at different angles by surrounding the patient with multiple detectors, tomographic images can be reconstructed using the theory of CT.

COINCIDENCE DATA QUALITY

The statistical quality of PET images is a function of the number of true coincidence events recorded over the course of data acquisition. Increasing the number of coincidence events acquired between the various detector pairs (lines of response) reduces the relative variability in each measurement and results in a less noisy image. A combination of the limited sensitivity of clinical scanners and restrictions on the amount of radioactive material that can be safely administered to patients means that PET scan durations are necessarily long compared with other imaging modalities like CT. Extending the scan duration improves the statistical quality of the measured data, but there are limitations imposed by the need for the patient to remain motionless for the duration of the study. Furthermore, the short physical half-life of isotopes such as ^{82}Rb (76 seconds) can mean that there is little gain in extended

scanning. Image noise can be reduced by the application of low-pass filters, but this invariably degrades spatial resolution. Much research effort has, therefore, been dedicated to improving the sensitivity of scanners so as to acquire more coincidence events in a given time period.

In addition to improving sensitivity, detector systems that improve the quality of the measured data (the kind of coincidence events) have also been developed. *True* coincidence events (“trues”) arise from pairs of photons that were produced from the same electron-positron annihilation and escape the body without undergoing further interactions. To contribute as a true event, both photons must be emitted in directions such that they are incident upon the detector system. For large-bore clinical systems, this excludes all but a small fraction of the emitted photons, resulting in a low sensitivity for true events. Annihilation photons that are emitted at angles so that only one photon reaches the detector result in single photon events that provide no useful image information. Single-photon detection events can also arise when one of the two photons is attenuated within the patient. The fact that coincidence detection requires both annihilation photons to escape the body increases the magnitude of the attenuation effect in PET compared with single-photon emission computed tomography (SPECT). This is true despite the fact that a single 511-keV photon has a lower probability of attenuation compared with the lower energy photons used in SPECT.

True coincidence events contribute useful information to the image but, in practice, these data are contaminated by the presence of other kinds of coincidence events (Fig. 3). In a typical clinical study, it is quite likely that two photons will be detected within the coincidence time window despite the fact that they did not arise from the same annihilation event. Such a situation occurs purely by chance and is increasingly likely as count rates are increased. The effect of such *random* coincidences is to introduce spurious counts along lines that do not necessarily pass through positron-emitting sources. They

contribute no useful information and, if uncorrected, will reduce image contrast and bias quantitative analysis.

Another source of unwanted coincidence events arises when one (or both) annihilation photons undergo Compton scattering interactions within the body but are still detected by the scanner. A line joining the points at which these photons were detected does not pass through the site of the annihilation event, and these data do not contribute useful information. This effect can be reduced by the use of energy discrimination as PET scanners measure not only the position of detected photons but their energy. Photons scattered through large angles emerge with significantly reduced energies and can be rejected by a lower level energy discriminator just below 511 keV. The limited energy resolution of current scanners is such that this lower level discriminator (LLD) cannot be set too high without rejecting too many unscattered photons that were erroneously recorded with an energy less than 511 keV. The LLD setting is therefore a compromise between rejecting unwanted scatter and accepting unscattered true coincidences. As the current generation of scanners has quite poor energy resolution, energy discrimination provides only limited scatter rejection and a significant scatter contribution remains. These *scatter* coincidences do not contribute useful information. They also reduce contrast and quantitative accuracy if not corrected.

The noise equivalent count rate (NECR) (2) is a figure of merit that has been developed to describe the quality of coincidence data that include true, random, and scattered components. It is equivalent to the coincidence count rate that would have the same noise properties as the measured trues rate after correcting for randoms and scatter. NECR is commonly used to characterize scanner performance and, since the relative proportion of the different kinds of coincidence events is strongly dependent on object size, standardized phantoms have been developed. For a given phantom, NECR is a function of the activity in the field of view and is usually determined over a wide activity range as a radioactive phantom decays (Fig. 4). The reason for

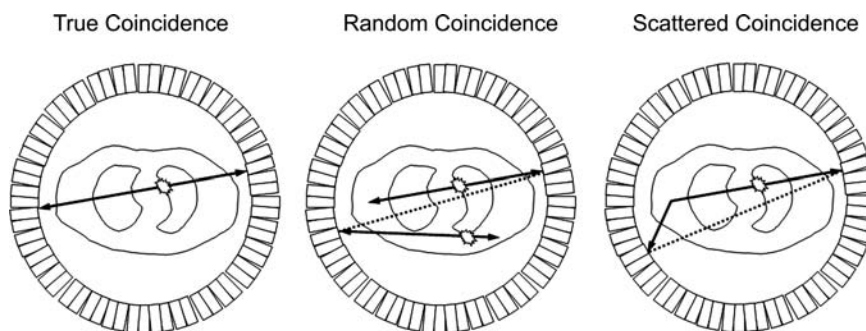


Figure 3 The coincidence events measured by a PET scanner can be true coincidences (*left*), random coincidences (*center*) or scattered coincidences (*right*). True coincidences contribute useful information to the image. Random and scattered coincidences provide no useful information and degrade contrast and quantitative accuracy.

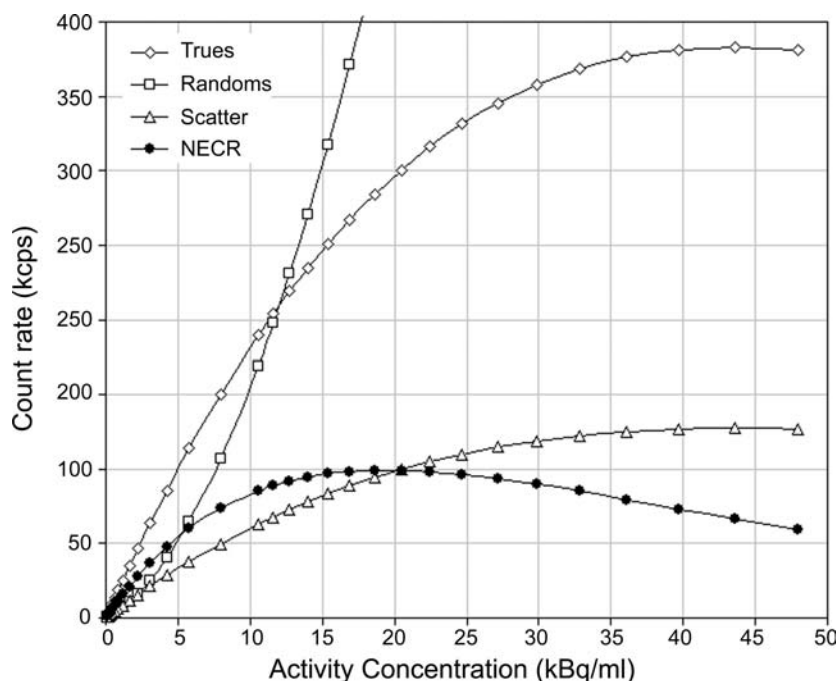


Figure 4 The relative proportion of true, random, and scattered coincidence events is a function of the activity in the field of view. As the activity increases, the trues count rate increases less rapidly because of detector dead time and the randoms count rate increases because of the greater number of photons being detected. The scatter count rate is assumed to be proportional to the trues rate. Scanner count rate performance can be characterized using noise equivalent count rate (NECR), which is a function of the true, random, and scatter coincidence count rates.

this count rate dependence is twofold: the randoms rate increases as the square of the single-photon count rate (which is approximately proportional to the activity in the field of view), and the sensitivity of the scanner for trues decreases with increasing count rates as detector dead time becomes more significant.

Dead time relates to the fixed amount of time required for the detector system to process an individual photon. During this time, the detector is not available to process any additional photons that may be incident upon it, and the sensitivity is effectively reduced. Detector dead time becomes increasingly significant at higher count rates and, beyond a certain point, both the trues count rate and the NECR curve decrease with increasing activity in the field of view. NECR curves can be used to compare scanner performance and, with certain caveats, can be used to determine the optimum administered activity that will minimize image noise in patient studies.

SCANNER DESIGN

PET scanner designs (3) continue to evolve as improved detector materials and configurations are developed. Despite this rapid evolution, most modern scanners share a common design that consists of a stationary ring of detectors that completely surrounds the patient in the

transverse plane. The diameter of the ring is usually large enough to accommodate any part of the body, although smaller scanners dedicated to a particular organ, such as the brain, have certain advantages. With the smaller diameter, sensitivity can be increased due to the larger solid angle of acceptance and spatial resolution can be improved as the noncollinearity of annihilation photons becomes less significant. The axial extent of the detectors in current whole-body scanners is typically of the order of 15 cm. However, there is a trend toward increasing the axial coverage. In the axial direction, the active area is broken down into a series of small detector elements in such a way that multiple thin slices are simultaneously acquired. Extended scanning in the axial direction, so as to acquire whole-body images, is achieved by translating the patient through the detector ring in a sequential manner. Whole-body scan durations are dependent on the required statistical quality of the images but are related inversely to the axial extent of the detectors. This in turn, is limited by cost considerations and, to some extent, patient tolerance of scanners with large tunnels.

Modern PET systems employ scintillation detectors coupled with an array of photomultiplier tubes (PMTs). These detectors have a high efficiency for absorbing 511-keV gamma photons and produce optical light that is converted by the PMTs to an electrical signal. The size

of each detector and the arrangement of the attached PMTs vary according to the scanner design. Some designs involve a small number of large detector panels, whereas others involve a larger number of small (approximately 4–5 cm), independent detector blocks. The block design tends to minimize detector dead time at high count rates because each block operates independently from the others. Large area panels, however, produce more uniform light collection across the face of the detector, which helps to maintain energy resolution. To improve the spatial resolution of the system, the size of the detector elements within each block or panel are made as small as possible, and there are invariably more detectors than PMTs. As a result, there is not a direct read-out of each detector element, and an incoming gamma photon produces signals in multiple PMTs. These PMT signals are combined so as to produce x and y coordinates in detector space and these data are used to map the event to a particular detector element. In addition to the effects of positron range and noncolinearity of annihilation radiation, the spatial resolution that can be achieved with PET is influenced by the size of the individual detector elements. Small detector elements give rise to high spatial resolution but, in order to maintain sensitivity for 511-keV annihilation radiation, the detectors are usually quite thick (2–3 cm). Although some scanners attempt to estimate a photon's depth of interaction within the detector, most scanners do not measure this quantity. For sources of activity close to the center of the field of view, this is not a significant problem because the resulting annihilation radiation is incident upon the detectors at approximately right angles and the depth of interaction is not important. However, activity toward the edge of the field of view is likely to be incident upon the detectors at more oblique angles. In these cases, the lack of depth of interaction information can cause events to be mispositioned, leading to a degradation of spatial resolution toward the edge of the field of view.

PET scanners have employed a wide range of different scintillating materials including bismuth germanate (BGO), gadolinium oxyorthosilicate (GSO) and lutetium oxyorthosilicate (LSO). LSO has emerged as one of the most effective scintillators, but new detector materials continue to be developed with the aim of improving the trade-offs between the properties of each crystal. Desirable properties include a high efficiency for stopping 511-keV photons, which is required to obtain low noise images in a short period of time. High light output allows the size of individual crystal elements to be reduced, thus improving the spatial resolution. Good intrinsic energy resolution is another important property of PET detector materials as it allows improved discrimination of low energy scattered photons from unscattered 511-keV photons. A further desirable property for PET detectors is the fast

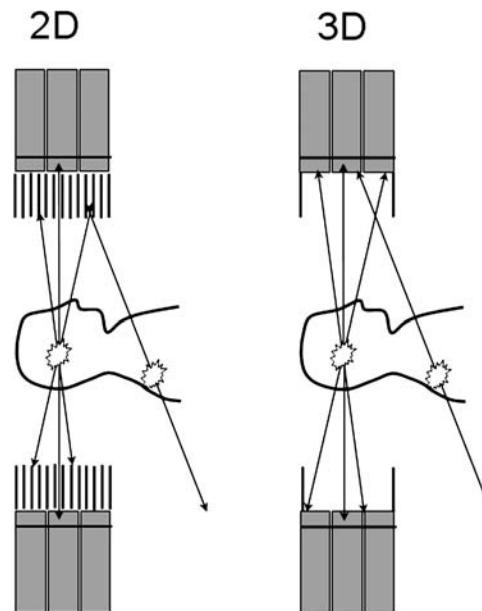


Figure 5 Illustration showing data acquisition with septa (*left*) and without septa (*right*). In 3D mode (*without septa*) sensitivity is increased compared with 2D mode (*with septa*) because of the greater solid angle of acceptance. However, in 3D, scatter is more significant and both randoms and dead time are greater (partly because of single photons from outside the coincidence field of view).

decay of the optical light that is produced when a photon is absorbed. This reduces detector dead time and allows the coincidence time window to be shortened, reducing the number of random coincidence events that are recorded.

In addition to energy discrimination, scatter can be reduced by inserting physical collimation in front of the detectors (Fig. 5). A series of thin annular septa, made of material such as tungsten, can be used to eliminate photons incident at large oblique angles to the detectors. Unlike the case of parallel-hole gamma camera collimators that provide collimation in two dimensions, PET septa provide collimation in only one dimension. They are not used to provide spatial information, but to reject scatter. The effect of the septa is to restrict photons incident upon the detector to only those traveling in an approximately transverse plane. Photons scattered within the patient may continue to travel in their original plane after the scattering event, but it is far more likely that they will scatter out of this transverse plane and be absorbed by the septa. The septa reduce the sensitivity of the scanner compared with an uncollimated system but also dramatically reduce the proportion of scatter. Scatter fractions of around 50% in the absence of septa can be reduced to around 15% with septa in place. Although both modes of operation can be used to produce similar

volumetric images, acquisition with the septa in place is referred to as 2D mode and acquisition without septa is referred to as 3D mode.

Determining the relative advantage of 2D and 3D acquisition remains a complex question. 3D acquisition provides a potential increase in sensitivity for true coincidences by a factor of around 5. However, this factor may not be realized in practice as the increased sensitivity of 3D mode results in greater count rates and higher detector dead time that reduces the effective sensitivity of the scanner. The higher count rates also give rise to greater contribution from randoms. In addition, both randoms and dead time are exacerbated by an increase in the detection of single photons from outside the coincidence field of view. Furthermore, as noted above, scatter is significantly higher in 3D than in 2D. The key to resolving this issue is the emergence of crystal materials such as LSO that combine high sensitivity for 511-keV photons with good energy and timing resolution. The improved energy resolution can be used to reduce the high scatter fraction in 3D by raising the lower level energy discriminator. The improved timing resolution can be used to reduce dead time and also to shorten the coincidence time window, reducing the randoms contribution. The result of these developments is that 3D acquisition can be used in conjunction with crystals such as LSO to reduce image noise with respect to 2D acquisition under certain circumstances.

A further advantage of detector materials that produce a rapidly decaying light signal is that this high temporal resolution potentially can be used to produce additional information about the location of an annihilation event. In conventional coincidence mode, an annihilation event is assumed to have taken place at some unknown location along the line joining the detectors. In *time-of-flight* mode, the time difference between the detection of corresponding photons is used to estimate where along the line, the annihilation event occurred. A hypothetical scanner with perfect temporal resolution, therefore, could measure the exact position of each annihilation event. There would be no need to reconstruct images from projections, and noise would be significantly reduced. In practice, the limited temporal resolution of current scanners means that time-of-flight mode can be used to localize individual coincidence events to a range of image space. The center of this range is dependent on the time difference between the detection of corresponding photons and the extent of the range is determined by the scanner's timing resolution, under the assumption that annihilation photons are traveling at the speed of light. The additional information provided by time-of-flight promises to improve image quality and motivates the development of faster detector materials.

IMAGE RECONSTRUCTION FROM PROJECTIONS

Coincidence events form the raw data used to reconstruct PET images. In the conventional mode of operation, the PET scanner adds coincidence events recorded between the same detector pairs (lines of response) in real time as the acquisition proceeds. These data are usually arranged into multiple projections where each projection consists of only those lines of response that are parallel to each other (Fig. 6). In the case of 2D acquisition, projections are one-dimensional data sets where each element of the projection is the number of coincidence events recorded along a particular line of response during the acquisition period. Full-ring PET scanners simultaneously measure multiple projections at different discrete angles around the patient. These different projections are often stored by the PET acquisition computer in data structures called sinograms. In the sinogram representation, 1D projections are stacked so as to form a 2D data set in which each row represents a projection acquired at a different angle with respect to the patient. The number of counts in each element of the sinogram (or projection) is approximately proportional to a line integral of the *in vivo* radionuclide distribution within the limitations of the various physical effects described previously. Corrections for these unwanted physical effects (randoms, scatter, etc.) are often incorporated into the reconstruction algorithm and these will be described in subsequent subsections. For the remainder of this subsection, we will provide an overview of the algorithms that convert these projection data to tomographic images.

Although 3D PET and multichannel spiral CT complicate the reconstruction issue considerably, in their simplest forms, PET and CT reconstruction problems are very similar. Numerous algorithms have been developed for reconstructing tomographic images (4), and they can be broadly divided into analytic and statistical approaches. Analytic algorithms of the type used in CT have been largely superseded in PET by statistical algorithms (also known as iterative algorithms). This replacement is because analytic algorithms, such as filtered back projection, were derived under the assumption that the measured projection data were ideal measurements with no noise. Such an assumption is particularly poor for PET data that typically have significant noise. Statistical algorithms such as ordered subsets expectation maximization (OSEM) (5) assume a more realistic Poisson noise model for the input data and have been found to have better noise properties than analytic algorithms in many imaging situations. Furthermore, statistical algorithms allow for the incorporation of various corrections into the reconstruction process, which has also been found to be beneficial in terms of image noise.

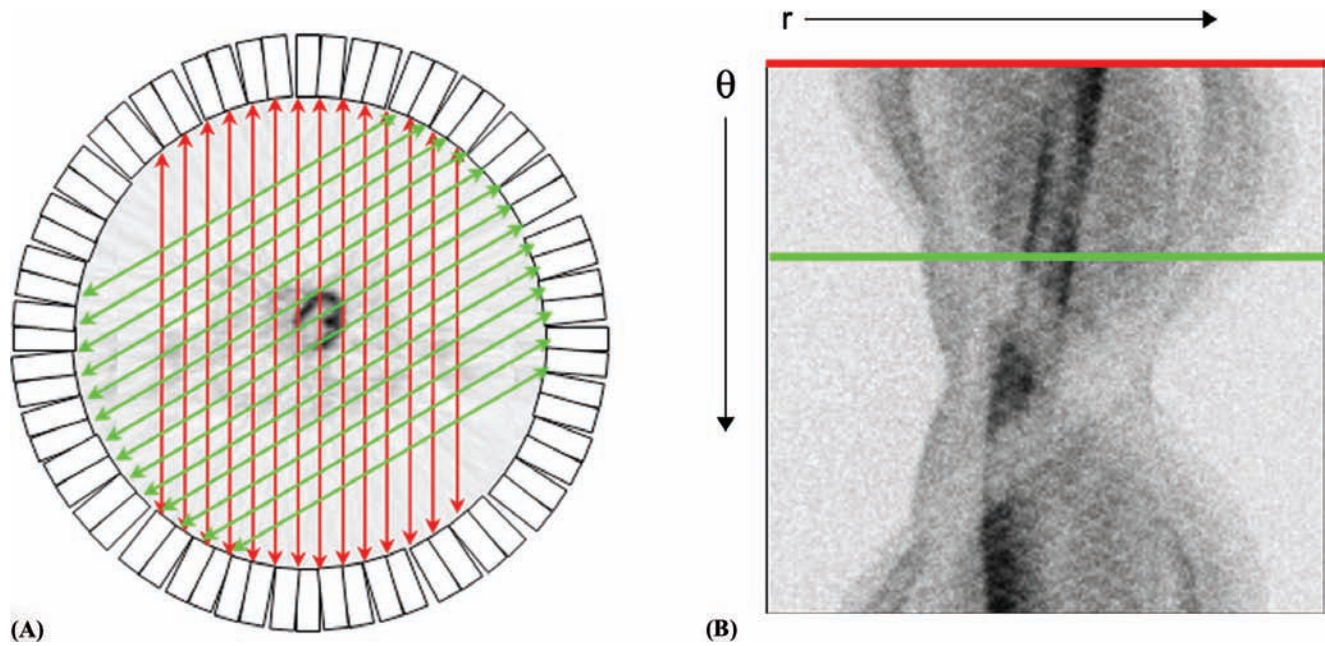


Figure 6 Full ring PET scanners simultaneously measure multiple projections at different angles with respect to the patient. **(A)** An example showing the orientation of two parallel projections. **(B)** An example of such projection data, which are typically stored in sinograms. In a sinogram each row represents a projection at a different angle θ . Each projection is made up of discrete elements that are indexed by r and contain the number of coincidence counts recorded along individual lines of response. The two example projections shown in **(A)** are also highlighted in sinogram **(B)**.

In general terms, statistical reconstruction algorithms are based on successively adjusting each pixel so as to produce an image that is most consistent with the measured projection data. The way in which the pixels are adjusted and the criteria for determining the most consistent image, are features that distinguish the different statistical reconstruction algorithms. Common to all statistical algorithms are a pair of software procedures that relate projection (or sinogram space) to image space and vice-versa. A back projector transforms projection data to image space by casting the number of counts in a particular projection element back into the image along the direction of the original measurement. A forward projector transforms an image to projection space by integrating the pixel values along parallel lines in the direction of the projection (analogous to the way the scanner produces projections of the activity distribution). These two operations are used together in an iterative manner to optimize the image estimate. The procedure starts by assuming some simple initial estimate that would not be expected to resemble the true image, such as an image of uniform intensity. This image is forward-projected to produce simulated projections that are compared with the measured data from the scanner to form an error projection. The comparison could be, for example, a ratio of the measured and simulated projections at each angle. The error sinogram is then back-projected into image space and used to adjust each pixel. A single iteration of this

procedure does not produce an accurate reconstruction but the process can be repeated with the updated image serving as the new image estimate. With each repetition of the procedure, the forward projection of the image estimate becomes increasingly similar to the scanner's measured projection data, and the updated image is assumed to be a better estimate of the true (unknown) image.

Noise in the measured projection data means that they will never be in perfect agreement with the simulated projections derived from forward-projecting the image estimate. For this reason, it is not obvious when to stop the iterative procedure. Stopping criteria are particularly relevant because insufficient iterations result in poor spatial resolution, and excessive iterations result in noisy images. For a particular patient study, there will be an optimum number of iterations that produces the best trade-off between noise and spatial resolution. This trade-off is likely to be dependent on patient-specific factors, the task in question and, in practice, the preference of the interpreting physician. Until recently statistical algorithms were prohibitively intensive of computational resources, and the clinical requirement for fast reconstruction times meant that analytical algorithms were preferred. Advances in processor technology and algorithm acceleration schemes such as ordered-subset implementations have meant that this issue is much less significant, and iterative algorithms have now been widely adopted for 2D studies.

For studies acquired in the 3D mode, the reconstruction problem is significantly more complex as data acquired at oblique angles with respect to the transverse plane have to be incorporated into the reconstruction. Instead of reconstructing a series of independent 2D slices, 3D data are used to directly reconstruct a volumetric image. Fully 3D reconstructions of this sort can be derived by extending the 2D algorithms described previously to three dimensions. The increased data volume that is involved in reconstructions of this sort gives rise to a large increase in reconstruction times, although these too, are now being routinely processed with 3D iterative algorithms.

As noted above, image noise and spatial resolution are a function of the number of iterations used in the iterative reconstruction. However, in many clinical protocols an additional smoothing filter is applied after completion of image reconstruction to further suppress noise. Low-pass filters of this sort reduce image noise but can easily obscure small lesions. The reason for this is related to a phenomenon called the partial volume effect that arises because of the limited spatial resolution of PET systems. When an object of interest is large compared with the spatial resolution of the system, its sharp edges will appear blurred in the reconstructed image, but the center of the object will still have an intensity that reflects the local activity concentration. However, for objects that are smaller than approximately twice the spatial resolution of the PET system (characterized by the full width at half maximum, FWHM, of a small point source), the blurring will be such that the image fails to recover the expected signal in the center of the object. This underestimation of image intensity for small objects is referred to as the partial volume effect and can be clearly illustrated with a phantom experiment (Fig. 7). A phantom consisting of

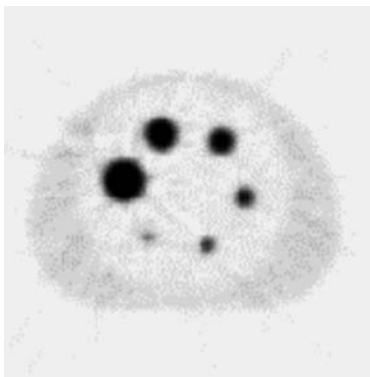


Figure 7 Image of a phantom containing 6 spheres of different sizes (internal diameter 37.1, 28.4, 22.2, 17.0, 12.6, 10.2 mm). Although each sphere was filled with the same concentration of activity, the reconstructed image shows the intensity in each region decreasing with sphere size. This partial volume effect arises because of the limited spatial resolution of the imaging system.

multiple small spheres of different dimensions can be filled with activity of the same concentration and placed in a uniform low background. Despite the fact that the activity concentration in each sphere is the same, the peak intensities of the spheres in the reconstructed image are proportional to the size of the spheres (for spheres smaller than twice the FWHM of the system). This is a significant effect in clinical imaging as it causes small objects such as tumors to be reconstructed with reduced intensity, and if excessive smoothing is applied, they may be completely erased. Note that in addition to this *point spread* phenomenon, partial volume problems are compounded by a different effect due to tissue heterogeneity. This *tissue fraction* effect refers to the averaging of signals that arises when a voxel contains a mixture of different tissue types. It is usually this latter phenomenon that is referred to as the partial volume effect in MRI and CT as these modalities have high transverse spatial resolution but potentially thick slices.

ATTENUATION CORRECTION

Of those annihilation photons emitted from within a patient, only a small fraction will escape the body without undergoing further interactions. Most photons will travel some variable distance before experiencing either Compton scattering or photoelectric absorption. Compton scattering is the most likely interaction mechanism for 511-keV photons in tissue, but once a photon has scattered, it emerges with a lower energy, and photoelectric absorption becomes more likely. Attenuation refers to the loss of photons within the body due to a combination of Compton scattering and photoelectric absorption. Even if only one of the annihilation photons is attenuated, the opportunity to measure a coincidence event will be lost and the number of trues recorded by the scanner will, therefore, be underestimated. The magnitude of this underestimate depends on the thickness and composition of the body tissue, and therefore it will be very different for each line of response through the patient. For a simple object such as a cylindrical water phantom, which has a uniform density and symmetrical shape, photon attenuation gives rise to an underestimate of the reconstructed image intensity that becomes progressively more significant toward the center of the phantom. The same trend is true for clinical images although, as patients have a nonsymmetrical body outline and nonuniform attenuation properties (particularly in the chest), the effect of photon attenuation on reconstructed images is more complex (Fig. 8) (6). If left uncorrected, photon attenuation leads to a loss of quantitative accuracy and characteristic artifacts that include an underestimate of image intensity toward the center of the body, an overestimate of the intensity of the skin, an overestimate of

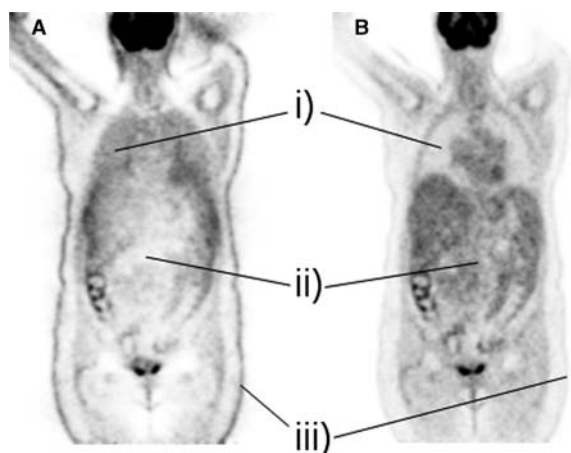


Figure 8 Corresponding coronal views of FDG PET images reconstructed without attenuation correction (A) and with attenuation correction (B). The image reconstructed without attenuation correction has characteristic artifacts that include (i) high uptake in the lungs; (ii) low uptake in the center of the body; and (iii) high uptake in the skin.

intensity in the lung, and artifacts in the heart, particularly in the anterior and inferior walls.

One of the advantages of detecting back-to-back annihilation radiation, as opposed to single photons, is the accuracy with which corrections can be applied for photon attenuation. This is so because, with PET, attenuation reduces the total number of coincidence events along any particular line of response by a simple factor that can be accurately measured. Although the average attenuation over all angles for a point deep within the body will be greater than a more peripheral point, for a particular line of response the attenuation experienced by a source of annihilation radiation is independent of its location along the line. This is because coincidence detection requires both annihilation photons to escape the body. Therefore, when considered together, the total thickness and composition of tissue through which the photons have to travel is not dependent on where along the line the annihilation event occurred. SPECT, in contrast, has a more complicated attenuation problem as each line of response measures single photons that experience different (unknown) degrees of attenuation on the basis of the depth within the body of their point of emission.

In PET, corrections for this effect can be determined for each patient study by measuring the attenuation properties of the tissue along every line of response. This can be achieved by incorporating a radioactive source into the PET gantry in such a way that it can rotate around the patient. This source is external to the patient and, in many cases, is a long-lived positron emitter such as $^{68}\text{Ge}/^{68}\text{Ga}$ (^{68}Ge decays with a half-life of 271 days to the positron emitter ^{68}Ga). By rotating this external

transmission source around the patient, attenuation factors can be calculated for each line of response by dividing the number of coincidence events recorded with the patient in the scanning position by the number of counts when nothing was in the field of view (blank scan). The attenuation experienced by an external 511-keV source is identical to that experienced by the internal 511-keV radiation because, as noted above, both back-to-back photons have to escape the body. Attenuation correction factors are simply the inverse of these attenuation factors and are applied to the measured emission projection data either before or during image reconstruction. Contamination of the transmission data with 511-keV emission photons from within the patient can be accounted for, and this method of attenuation correction is extremely accurate, provided the patient does not move between the transmission and emission acquisitions.

Although radionuclide transmission sources can be used to provide accurate attenuation correction, they require additional scans that add significantly to the overall duration of the imaging procedure. The blank scan can be acquired with high statistical accuracy when the scanner is not in clinical use and so does not add to the duration of patient studies. However, the transmission scan performed with the patient on the imaging table has to be acquired for a period of time similar to that used for the emission acquisition. The reason for this is that statistical noise in the measured transmission data propagates through to the emission image via the attenuation correction procedure. In order to maintain the statistical quality of the attenuation-corrected emission data, transmission scans have to have low noise, and this can usually only be achieved by lengthy scanning. The exact time required for transmission acquisition is dependent upon the activity of the transmission sources, the size of the patient and the anatomic region of interest but is typically in excess of 3 minutes per bed position. Shorter scan durations may be feasible if transmission image segmentation is performed. This image processing procedure reduces noise in the measured transmission data by exploiting the fact that the different tissues of the body have only a limited range of (approximately) predictable attenuation values for 511-keV photons. Further reductions in transmission scan durations can be achieved by using external sources that give rise to single photons as opposed to positrons, e.g., ^{137}Cs decays, with a half-life of 30 years to the single photon emitter $^{137\text{m}}\text{Ba}$ (662 keV). Higher activities of single-photon emitters can be employed, as the detector closest to the source on the near side of the patient is not used in this mode of acquisition. The transmission source can be shielded from the nearby detectors, thus reducing the dead time issues that limit the amount of activity that can be used with positron-emitting transmission sources.

The introduction of combined PET/CT scanners has effectively eliminated the need for radionuclide transmission scans as the CT data can be used to compensate for photon attenuation (7). Although delivering a higher radiation dose compared with radionuclide transmission sources to the patient, CT can be acquired in a much shorter period, producing attenuation correction factors with very low noise. This process has significantly reduced the overall scan duration for attenuation-corrected PET studies, particularly whole-body scans that require an extended axial field of view. Because they are acquired using X rays with a spectrum of energies around 30 to 140 keV, CT images have to be transformed to reflect the different attenuation properties of the 511-keV photons used in PET. This transformation frequently takes the form of a rescaling of the CT image, although a single scaling factor is not effective at handling both soft tissue and bone regions. Bilinear scaling or a combination of image segmentation and scaling has been found to produce adequate quantitative accuracy for most applications. Additional complexity can be introduced by the presence of CT contrast material that can alter Hounsfield units significantly and, in the case of intravenous contrast, may be present with different concentrations at the times of CT and PET acquisition. Metallic implants can also create artifacts in the CT that, if not corrected, can propagate through to the PET via the attenuation correction.

Note that attenuation correction eliminates the artifacts that are introduced by photon attenuation and helps restore quantitative accuracy, but it does not recover the loss of statistical quality that is a consequence of a reduced number of photons escaping the patient. The largest attenuation correction factors are applied to the most heavily attenuated projections, and these are also likely to be the noisiest projections. Boosting the relative contribution of the noisiest projections in this way can potentially amplify noise in the reconstructed images. Attenuation-weighted reconstruction algorithms reduce this kind of noise amplification by incorporating the attenuation correction into the iterative reconstruction process. However, this process does not address the underlying problem that limits PET image quality, the problem of large, high-attenuation patients leading to a relatively small number of photons escaping the body and correspondingly high image noise. The image quality can only be improved by increasing the duration of the acquisition in proportion to the patient's weight or, if the count rate performance of the scanner permits, increasing the administered activity.

OTHER CORRECTIONS

In addition to attenuation correction, numerous other corrections are applied to the measured coincidence data prior

to or during image reconstruction. These include corrections for randoms, dead time, scatter, and radioactive decay.

Randoms Correction

Corruption of the measured data by random coincidence events can be corrected using methods based on either a delayed coincidence channel or detector singles rates. Using the former approach, the photons detected by the scanner are processed so as to produce a secondary set of coincidence data. In this secondary channel, the timing signal of one of the detectors is intentionally delayed with respect to the other, such that true (including scatter) coincidence events cannot be recorded within the scanner's coincidence timing window. Although true coincidence events cannot be recorded in this *delayed* channel, the artificially introduced time delay does not prevent two photons from unrelated annihilation events being detected within the coincidence timing window. These data are a very good estimate of the unknown number of random coincidence events recorded in the principle, nondelayed (or prompt) coincidence window. Randoms correction can be implemented by direct subtraction of the delayed data from the prompt data, either as the acquisition proceeds or as a postprocessing procedure. One disadvantage of the delayed event channel method is that it frequently records only a small number of coincidence events per line of response and subtraction of this noisy randoms estimate degrades the statistical quality of the corrected data. In order to reduce the noise introduced by this method of randoms correction, an alternative approach can be used on the basis of single photon event rates at each detector. Measurements of the single photon event rates at all detectors and knowledge of the coincidence timing window can be used to estimate the randoms contribution that can be expected in the measured coincidence data. This method has the advantage that because the singles rates are much higher than the delayed coincidence rates, the resulting randoms estimate has very low noise. Note that randoms correction can potentially lead to negative pixel values if noise in the measured data is such that the randoms estimate exceeds the number of counts in the prompt window. This is not usually a problem and randoms correction is essential for accurate image quantification.

Dead Time Correction

The individual detector modules within a PET scanner require a finite period of time to process each detected photon. If a second photon is incident upon a detector while an earlier photon is still being processed, the secondary photon will be lost. Dead time correction compensates for this loss of sensitivity that becomes increasingly

significant at high count rates. A global correction factor can be applied to all data from a particular acquisition on the assumption that dead time effects were similar for all detectors in the ring. Alternatively, different corrections can be applied to each detector block or group of blocks. Corrections can be determined on the basis of an estimate of the fraction of the acquisition period that each detector was busy processing events and unable to process other photons. As a third option, the single photon rate at a particular detector can be used in conjunction with a model of the scanner's dead time performance to estimate the magnitude of the dead time effect. Although pile-up of scintillation light from separate photons detected at nearby locations (at approximately the same time) can cause event mispositioning, dead time correction only compensates for count losses. Unlike attenuation correction, dead time correction does not typically alter the appearance of the image but it does improve quantitative accuracy. As such, it is important for quantitative dynamic studies where the dead time factors may change over the course of the acquisition. It can also be important for clinical oncology studies that measure indices of tumor metabolism, particularly for high sensitivity 3D scanners.

Scatter Correction

Scatter correction is required because the limited energy resolution of current PET systems means that scattered photons can be only partially rejected by energy discrimination. Uncorrected scatter forms a background in reconstructed images that reduces lesion contrast and degrades quantitative accuracy. This scatter background is a complex function of both the emission and attenuation distributions and is nonuniform across the field of view. In 2D mode, physical collimation ensures that the scatter contribution is relatively low compared with 3D. Approximate corrections, based on scatter deconvolution, have been widely used. The form of the scatter distribution function can be measured experimentally using line sources at different positions in a water phantom and deconvolved from patient data to obtain an estimate of the true coincidence events. This method assumes a uniform scattering medium and has limited accuracy in areas such as the thorax. It also cannot account for scatter from outside the field of view of the scanner, which can be significant for 3D acquisition. An alternative algorithm that has been applied to 3D brain studies involves a tail-fitting approach. In brain studies, the lines of response that do not pass through the head comprise scatter that can be modeled by fitting a Gaussian function to the tails of each projection. This function can be interpolated to the projections that do pass through the head and used as an estimate of the scatter contribution along these lines of

response. This method provides a first-order correction for scatter and has limited accuracy in areas of nonuniform attenuation or any area where the tails of the projections cannot be accurately measured. More accurate scatter correction can be achieved in 3D using a model-based approach (8). This method makes use of the transmission data, emission data, and the physics of Compton scattering to model the distribution of coincidence events for which one of the two photons experienced a single scattering interaction. The assumption that the scatter component in the measured data is dominated by events in which only one photon has experienced a single Compton interaction has been shown to be reasonable. Furthermore, a model of multiple scatters can be incorporated, and the resulting estimate of the scatter distribution has been found to be highly accurate over a range of anatomical locations.

Decay Correction

The above corrections are applied to the projection data at the time of reconstruction and generally involve the application of unique correction factors for each individual line of response. Decay correction is a simpler procedure that is applied to the image data after reconstruction. It involves adjusting all pixel values in a particular image by a scale factor that accounts for physical decay of the isotope during the time of the acquisition. The decay correction factor is the same for all images acquired at a particular bed position, and so it has no effect on the appearance of the image. Although decay correction does not affect image quality, it is essential for most quantitative studies and also for multiple bed-position studies such as whole-body scans. Failure to apply decay correction in FDG whole-body studies typically results in marked discontinuities at the joint between images acquired at different bed positions. These discontinuities are due to the physical decay of ^{18}F during the course of data acquisition at each bed position and results in fewer disintegrations per unit time with each successive bed position.

PATIENT MOTION ISSUES

As with other imaging modalities, patient motion during data acquisition introduces a blurring effect that degrades image quality and may obscure detection of small lesions. In addition to this obvious effect, motion can cause the PET emission data to become spatially misaligned with the transmission data acquired for attenuation correction. On a PET/CT scanner this means that the two images are not just misregistered with respect to each other but that the PET images may have artifacts introduced by inaccurate attenuation correction. This inaccuracy is a particular

problem around the lung boundary as the lungs and surrounding soft tissue have very different attenuation properties. If, for example, motion caused part of the heart in the PET image to extend into the lungs in the CT image, that portion of the myocardium will be under-corrected for attenuation and could be mistaken for a defect in the heart wall. Similar artifacts can also occur in oncology studies, particularly at the dome of the liver where respiratory motion can often cause misregistration of the PET and CT data. Brain studies are also susceptible to motion problems as the use of misregistered CT for attenuation correction can introduce systematic side-to-side or front-to-back bias in the reconstructed PET image.

Identifying motion-induced errors in attenuation correction is very important and the spatial alignment of PET/CT images should be carefully checked before reading. For brain studies it may be possible to circumvent motion-induced attenuation correction problems by using an alternative approach to attenuation correction that does not require transmission data. Calculated attenuation correction is based on an estimate of the skull boundary determined on the non-attenuation-corrected PET images and assumed values for brain attenuation. In some situations, artifacts due to misregistration of the PET and CT (or other transmission) data can be approximately corrected by software registration. The alignment of non-attenuation-corrected PET and CT images can be adjusted and the resulting data used to improve the accuracy of the attenuation correction. This approach has been effective for cardiac studies that involve a limited field of view and predictable anatomic area of interest. For whole-body studies, this approach may not always be practical, and in these cases, PET images reconstructed without attenuation correction can sometimes be useful. Despite the characteristic artifacts associated with non-attenuation-corrected images, these data can often be used to resolve confusion in cases where the accuracy of the attenuation-corrected images is questionable. Although careful patient setup can reduce the likelihood of gross motion problems, indiscriminate movement of, for example, the arms or head can be difficult to correct and may require the study to be repeated.

Predictable motion associated with the cardiac and respiratory cycles can be managed by performing the acquisition in conjunction with an appropriate monitoring device. Electrocardiogram (ECG) machines or devices for tracking respiratory motion produce trigger signals at specific points in their respective cycles and these triggers can be supplied to the PET scanner during data acquisition. In order to acquire data with sufficient statistical quality, PET studies necessarily involve data acquisition over many respiratory or cardiac cycles, but these trigger signals allow data acquired during corresponding phases

to be combined. An externally triggered or *gated* acquisition would divide the cycle into a specific number of phases and produce a series of images where each image represents a different phase of the motion. These data can be displayed sequentially in a cine mode, although a common problem is that each gated image is acquired for only a fraction of the total acquisition time and frequently contains high noise. For certain studies involving long-lived isotopes, this problem can be avoided by extending the scan duration, although this may not be practical for multibed position respiratory gated studies. Also for ECG-gated studies involving isotopes such as ^{82}Rb , extended scanning provides little gain because of the short 76-second half-life of the isotope.

Gated acquisition (either cardiac or respiratory) is supported on many scanners via a mode of acquisition referred to as *list mode*. List mode acquisition differs from the more conventional *frame mode* in that each coincidence event is not immediately sorted into a sinogram. Instead, the location of each coincidence event is stored as a stream of data along with regular timing signals and trigger signals from an ECG or respiratory gating device. The advantage of list mode is that it allows flexible, retrospective sorting of the data into static (all data combined), dynamic (multiple time series frames), or gated (multiple frames based on ECG or respiratory triggers) sinograms. Any combination of these data is possible allowing, for example, both ECG-gated and dynamic cardiac images to be obtained from a single list mode acquisition. Furthermore, because the sorting is performed retrospectively, parameters such as the number of images in a gated sequence can be defined after the acquisition. This situation is in contrast to frame mode in which all acquisition parameters have to be specified when the scan is configured.

IMAGE QUANTIFICATION

Although there is extensive research literature describing the use of PET to quantify such things as blood flow or glucose metabolism in absolute terms, this potential has not been fully exploited in routine clinical practice. The reason for this is that, compared with current clinical protocols, quantitative PET protocols are usually only possible over a limited field of view; they are invariably more complex and time consuming; and data analysis is typically more involved. Furthermore, the clinical benefit of augmenting visual analysis with additional quantitative data of this sort has not been demonstrated. The use of the standardized uptake value (SUV) to quantify glucose metabolism in FDG oncology studies has been particularly controversial (9), although its use has become widespread. This widespread use is largely due to its compatibility with standard

whole-body protocols and the ease with which it can be calculated. In its simplest form, SUV is defined as follows:

$$\text{SUV} = \frac{\text{Tissue activity concentration}}{\text{Injected activity/Patient mass}}$$

The tissue activity concentration is obtained from the PET image and these data must, therefore, be corrected for physical effects (e.g., attenuation, scatter) and calibrated in units of radioactivity concentration (decay corrected back to injection time not scan start time). Additional study-specific factors such as the amount of activity administered, the time of administration and the mass of the patient also need to be recorded. In an effort to standardize data across patients with different amounts of body fat, the lean body mass, which requires a measurement of the patient's height, has also been used. SUV is sometimes referred to as a semiquantitative index of glucose metabolism to distinguish it from more rigorous methods that quantify metabolism in absolute terms by simultaneously measuring the concentration of tracer in both tissue and blood as a function of time.

Although SUV is a simple parameter to calculate, it requires additional quality assurance on every patient study where it is to be used. SUV cannot be accurately determined from studies where the attenuation or decay correction is suspect or from those that resulted in a tissue injection of tracer. Before calculating SUV for tumor or other organs of interest, the SUV of normal tissues (e.g., liver) should be checked to confirm that they lie within the expected range. If in doubt, the accuracy of the manually entered patient data should be checked, along with the times of the injection and scan start (especially around time changes due to daylight savings). Although the delay between tracer injection and the start of scanning for optimum SUV determination is likely to be dictated by the purpose of the study, individual centers frequently standardize at some point between 45 and 60 minutes. Establishing a fixed postinjection delay reduces the variability of SUVs and increases the validity of comparing data determined at different scanning sessions (e.g., pretreatment and posttreatment). The dynamic nature of FDG kinetics in tumor means that SUVs may be significantly biased if calculated from scans acquired at different post-injection delays and, therefore, may not be comparable.

As with other forms of PET image analysis, SUV data are susceptible to the partial volume effect. This susceptibility means that the SUV calculated for small tumors is likely to significantly underestimate the true SUV that would have been calculated had the scanner had perfect spatial resolution. In practice, tumors that are smaller than around double the spatial resolution of the system will be underestimated. Note that this spatial resolution is the resolution achieved in the clinical images and is likely to be much larger than the best-case values measured during system testing. The magnitude of the partial volume effect

is also influenced by the way in which regions of interest (ROIs) are defined. Large ROIs that encompass the whole lesion average out the signal from heterogeneous tumors and are also more susceptible to the partial volume effect. ROIs that are smaller than the size of the tumor and are centered on the pixel with the maximum intensity reflect the most metabolically active part of the tumor and are less affected by the partial volume effect. However, both approaches require ROIs to be carefully defined, and this subjective and time-consuming procedure is often avoided by recording the maximum SUV in the tumor. This approach is not dependent on subjective ROI definition, is least biased by partial volume effects but is more prone to statistical variability due to the small, single pixel region of the image that is used. In principle it is possible to correct SUVs for the partial volume effect using recovery coefficients determined from phantom experiments. However, corrections of this sort are often inaccurate for small tumors as they are crucially dependent on the size of the metabolically active part of the tumor, which is often hard to measure accurately.

SCANNER QUALITY ASSURANCE

Scanner quality assurance (QA) encompasses a range of procedures that are performed in order to ensure that the instrument is operating optimally. Establishing a program of QA, which is performed on a regular basis, is essential to eliminate many kinds of avoidable image artifacts, quantitative errors, and more serious failures to acquire interpretable data. The importance of performing QA procedures in both a frequent and consistent manner is as important in PET as it is in other modalities. Not only does routine QA minimize the likelihood of image artifacts, but documenting QA results provides verifiable evidence that the scanner was operating as expected. A large number of procedures can potentially be performed, and the type and frequency of QA varies between institutions. This variation reflects differences in the type of institutions, scanner designs, range of studies performed, and the regulatory requirements in different countries. In general, QA procedures can be divided into those that update scanner calibrations and those that test performance. The tests of system performance can be further divided into those performed at the time of installation, those performed on a daily basis, and those performed on a less frequent basis (e.g., monthly, quarterly, or annually). It should be noted that as PET instrumentation has developed, scanner QA has necessarily changed to reflect these advances. Examples include measurements of spatial alignment between PET and CT images in a combined scanner and timing calibration in a time-of-flight scanner.

Because the components of a scanner may drift over time, it is important to update the scanner's calibrations in

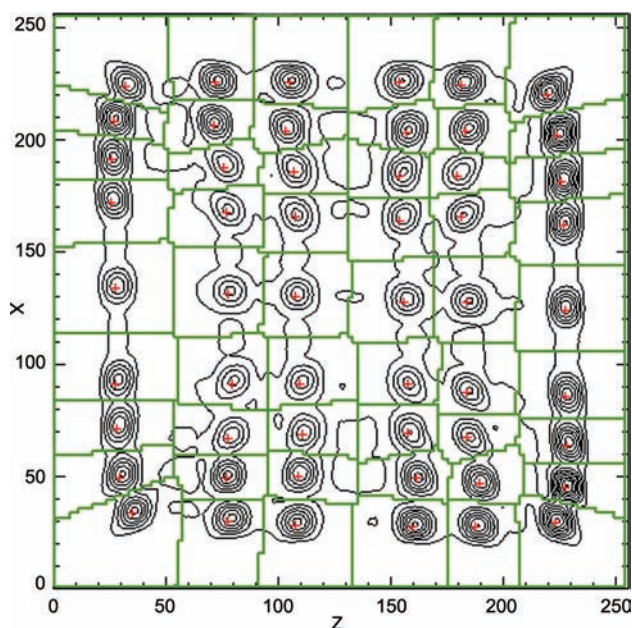


Figure 9 Position calibration is required because in modern PET systems there is not a one-to-one coupling of detector elements and PMTs. Exposing a detector block to a uniform flood of 511-keV photons produces a series of nonlinearly spaced peaks corresponding to the individual detector elements. Position calibration characterizes each detector block so as to produce a linear spatial response. *Source:* Courtesy of General Electric Healthcare (Waukesha, Wisconsin, U.S.).

a regular fashion. Routine maintenance is typically performed on a quarterly basis although more frequent recalibration may be required after hardware changes. The nature of these procedures is different for each manufacturer but typically includes detector position calibration, energy calibration, and coincidence time calibration. Position calibration translates the signal produced by each detector block or panel to a particular crystal element within that block or panel (Fig. 9). It is an experimentally determined lookup table for all detectors in the scanner and ensures a linear spatial response across the face of the detector. Energy calibration is necessary because variations in the response of the different detectors cause the measured position of the 511-keV photopeak to vary from detector to detector. To compensate for these variations, energy calibration determines the peak channel in the energy spectra for each individual detector element and uses this to define upper and lower energy thresholds that are specific for each detector. The above calibrations refer to single-photon detection, but when operating in coincidence mode, an additional time calibration is required. This calibration compensates for time differences between detector pairs as a result of differences in the temporal responses of the PMTs and readout electronics.

The calibrations discussed above are calculated periodically and applied to all subsequent data in *real time* as each acquisition proceeds. Normalization refers to a correction that is applied to the sinogram data after acquisition has been completed but before (or during) image reconstruction. It compensates for the nonuniform response of the different detector pairs when operating in coincidence mode. This nonuniformity is a result of variations in the efficiency of individual detectors and also geometric factors. A number of geometric factors affect the sensitivity of coincidence data, including the angle of incidence the photons make with the detectors and the location of the detector elements within the larger detector block. Normalization files consist of separate correction factors for each line of response and are recalculated following changes to the detectors or the detector calibrations. Because they reflect geometric factors, separate normalization files need to be calculated for both 2D and 3D modes of acquisition. Normalization files are determined experimentally and can require lengthy acquisition periods to reduce noise in the measured correction factors to acceptable levels. Failure to acquire normalization data with adequate statistical quality can result in characteristic artifacts that will be present in all subsequent images. This can sometimes occur if the sources used to determine the normalization had too low activity or the duration of the normalization scan was cut short. Following an update of the normalization files, it is necessary to recalculate the calibration factors that convert the reconstructed images from arbitrary units to activity concentration (kBq/mL). This recalibration can be achieved by scanning a uniform phantom with a known activity concentration in both 2D and 3D modes (where applicable). The accuracy of this calibration is highly dependent on the accuracy of the dose calibrator used to measure the phantom activity, and QA programs should therefore include testing of this related equipment.

Although not mandatory, many centers require a detailed performance evaluation of new systems after initial installation but before the first patient study (acceptance testing). Tests of this sort can help identify problems with a particular installation and also bring to light limitations of the scanner's capability that might not have been previously realized. The tests recommended at the time of installation include measurements of spatial resolution, count rate performance, sensitivity, quantitative accuracy, and image quality. Standard methods for performing these tests (10) allow comparison of the results with the manufacturer's specifications and literature data. In addition to confirming satisfactory installation, these measurements can be used as a benchmark against which subsequent measurements can be compared. The occasions where it might be necessary to repeat these measurements include hardware or software alterations and

relocation of the equipment. Repeating these detailed tests daily is not practical, and more convenient tests are required for routine QA.

Daily QA of PET scanners prior to clinical imaging is essential, but the details of the specific tests vary according to the manufacturer. In general the recommended procedure for daily use involves a test of the sensitivity of the detectors. This test can identify individual detectors that have become unreliable and overall drift in the sensitivity of the scanner over time. It can be conveniently performed using long-lived isotopes such as ^{68}Ge (271-day half-life) or ^{22}Na (2.6-year half-life) that can be in the form of point sources or cylinders filled with a uniform distribution of activity (commonly 20-cm diameter). Alternatively, some scanners incorporate ^{68}Ge pin sources that rotate around the gantry providing the detectors with a low-scatter flux of radiation. Such systems have the advantage of being convenient and reproducible but, like the ^{68}Ge cylinder source, require periodic replacement. The resulting data may be in the form of sinograms or individual detector measurements, and visual inspection is often adequate to identify detectors that have failed. Quantitative analysis of these data can be used to alert operators to detector problems and also allows the performance of the detectors to be monitored as a function of time. In some cases additional detector data are available including the peak energy channel, timing error, and dead time.

Note that the daily QA procedures described above test only the detectors and not the overall performance of the system. Numerous other factors influence scanner performance, including normalization, image reconstruction and corrections for attenuation, scatter, randoms, and dead time. Testing of individual components may be necessary if a problem is suspected but an overall evaluation of the system is possible by scanning simple phantoms. Phantoms that have been used include 20-cm diameter cylinders that may be filled with radioactive water or consist of a resin containing a uniform distribution of ^{68}Ge . In addition to uniform phantoms, cylinders and larger torso phantoms with inserts of different sizes have been used. Although phantoms of this sort are not representative of the attenuation and scatter distributions encountered in body imaging, they provide a convenient reference that can help confirm that the scanner is performing consistently. Visual analysis of phantom images can help eliminate major problems and ROI analysis can assess quantitative accuracy and resolution recovery. The ability to reconstruct an artifact-free image of a uniform phantom with a mean SUV of approximately 1 is a prerequisite for subsequent quantitative analysis of patient images. If, in addition to the uniform region, the phantom contained inserts of different sizes with

higher concentrations of activity, a simultaneous assessment of spatial resolution can also be made. Depending on the site, tests of this sort may be performed on a daily, monthly, or quarterly basis. Data acquisition and processing should be performed with the protocols used for clinical studies and, where both 2D and 3D acquisitions are employed, both modes should be evaluated.

CONCLUSION

PET instrumentation is developing at a rapid rate with a number of significant advances in detector technology, data processing, and image reconstruction. A major development has been the merging of PET with CT in a combined scanner that allows functional PET data to be fused with high resolution anatomical CT. Ongoing developments in instrumentation continue to improve spatial resolution, reduce image noise, and open new avenues for multimodality imaging. These factors, combined with the favorable chemical properties of many positron-emitting isotopes, provide PET with a strong methodological basis.

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3

Patient Preparation and Scanning Considerations for PET and PET/CT

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INTRODUCTION

Little data are available on the true impact of positron emission tomography/computed tomography (PET/CT) imaging on diagnostic accuracy and patient management (1,2). Since acquisition of CT in PET/CT is still considered suboptimal as a diagnostic tool, PET/CT protocols generally use reduced dose settings for attenuation correction and for anatomic labeling of PET findings (1,2). However, an increasing number of users believe that PET/CT can replace a clinical CT and a clinical PET. Therefore, to perform a state-of-the-art diagnostic CT, oral or intravenous (IV) contrast agents are administered to maximize the diagnostic information on anatomy and tumor vascularization (3).

PET/CT PROTOCOL CONSIDERATIONS

Patient Preparation

Patient preparation is a team effort that begins with the scan scheduler and is followed up with the nurse and with the technologist. Potential problems, e.g., diabetes and medications, are dealt with ahead of time so that protocols can be tailored to individual needs.

At the initial intake (Table 1) of the patient, the height and weight of the patient are verified, the time and content of the patient's most recent meal is ascertained, and the

Table 1 Pre-Scan Preparation Protocol for Oncology PET/CT Studies

Obtain height and weight of patient using scale in PET preparation room.
Ask patient if they have had anything to eat or drink 4 hr prior to study.
Ask all female patients of child-bearing age if possibility of pregnancy.
Start an IV using a 22- or 24-gauge angiocatheter in patient's arm (contralateral arm if prior surgery).
Test the blood glucose, if level is >150 mg/dL, or <80 mg/dL (refer to chart), consult the physician.

possibility of pregnancy is reviewed with all female patients of child bearing age. At this point a stable, 22- or 24-gauge IV catheter is placed in a peripheral vein. Blood glucose is tested to ensure that the level is between 80 and 150 mg/dL. Unless contraindicated as in patients with known or suspected head and neck cancer, dilute oral barium contrast (1.2%) is administered prior to injection of the radiotracer (Table 2). The total amount of oral contrast is adjusted to patient size and is divided into two doses: one administered prior to the radiotracer, and a smaller portion given at the end of the radiotracer uptake phase to ensure contrast in the stomach and proximal small bowel.

Table 2 Oral Contrast Administration

If indicated, have patient drink READI-CAT 1.2% barium sulfate oral contrast (not flavored):

If the patient weighs less than 150 lb, give 1.5 bottles prior to injection of FDG and ½ bottle 30 min post FDG injection (30 min before imaging).

If the patient weighs more than 150 lb, give 2 bottles prior to injection of FDG and 1 bottle 30 min post FDG injection uptake phase (30 min before imaging).

30 min after injection, an additional ½ bottle of contrast is administered.

Have patient drink ½ a cup of water to clear oral pharynx of barium prior to scan.

¹⁸FDG is administered through the IV catheter, whenever possible, to limit personnel radiation dose, to decrease the chance of dose infiltration, and to minimize patient discomfort. Dosing is influenced by patient weight in both children and adults (Table 3). The pediatric dose of FDG is 0.22 mCi/kg. Uptake periods suggested vary, but most commonly hover between 45 and 60 minutes. More prolonged periods of uptake have been suggested to improve sensitivity for tumor (4–6) but the advantages in using delayed scans to differentiate benign false positives from malignant tumors is more controversial (7,8).

During the uptake phase the IV catheter is left in place for diabetic patients and for those in whom IV contrast administration is planned. The patients are asked to sit quietly with their legs uncrossed and arms resting at their sides. For patients in whom the oropharynx and neck are a particular concern, talking and swallowing are strongly discouraged. For patients undergoing brain scans, the rooms are kept only dimly lit, for oncologic studies this is less critical. Approximately, 15 minutes prior to the start of the scan (and 30 minutes after the radiotracer injection), the remaining oral contrast is administered. Just prior to the scan, patients are asked to empty their bladder and a check is made to ensure that all metallic materials have been removed from the area of the body being scanned (e.g., zippers, removable bracelets, fashion items, piercings).

Scan Acquisition

A typical oncology study protocol is described in Table 4. Brain protocols vary mostly in terms of positioning of the head. Similarly, for head and neck studies, CT and PET are acquired with the arms down to limit the attenuation

effects of the arms. For studies where pelvic pathology is of particular concern, a delayed post-void acquisition of the pelvis may be performed. Bladder catheterization may be performed, but is not done so routinely.

CT Contrast

There is general consensus about the benefit of the contrast-enhanced approach CT over the nonenhanced CT protocol. Violante et al. (9) demonstrated an increase in accuracy for detection of liver lesions from 63% to 90% when applying IV contrast agents. Using IV and oral CT contrast agents, anatomic structures can be better delineated and sensitivity and accuracy of CT in lesion characterization can be increased. There is controversy about the use of CT contrast agents in dual-modality PET/CT, since it is still not clear if a fully diagnostic CT examination is needed as part of the PET/CT evaluation or if it can be achieved with current CT protocols. Since an optimized contrast protocol for CT must image different body regions in region-specific phases of contrast enhancement (e.g., the thorax should be scanned in the arterial phase, whereas the upper abdomen should be imaged in the portal-venous phase), choosing the proper timing, rate of injection, and even amount of IV contrast can be problematic for PET/CT. Protocols offering acquisition of more than one CT spiral in combination with PET have already been proposed (10), but they are far from been routinely used. This issue has been dealt with in more detail in chapter 1, “Technical Aspects of CT in Practice,” but the effects on the PET scan require some adjustment in the timing of the contrast injection relative to the start of the CT. In our practice, we wait 70 seconds before the injection of approximately 100 cc of nonionic, iodinated, low-osmolar contrast agent with a rate of 2 cc/sec. However, recently, several intravenous contrast-enhanced protocols have been compared to see which protocol was able to achieve PET images free of contrast-related artifacts. Only the protocol using a dual-phase injection (80 and 60 mL at 3 and 1.5 mL/sec, respectively) in the caudocranial direction with a 50-second delay yielded high-quality whole-body PET/CT images without generating intravenous contrast-related artifacts in either the CT or the PET image volume (11). However, the study in

Table 3 Dose Determination for ¹⁸FDG

Adult dose (oncologic indications):

Standard dose 15–20 mCi (555–740 MBq) in adults.

Maximum dose is 25 mCi with weights >114 kg or 250 lb.

Minimum dose is 5 mCi with weights <23 kg or 51 lb.

Brain study dose: 10 mCi

Pediatric dose:

0.22 mCi/kg up to standard adult dose

Table 4 Sample PET/CT Acquisition Parameters

CT scan
Acquire topogram:
Direction: caudocranial
Tube current: 50 mA
Tube voltage: 120 kV
Acquire CT scan:
Direction: caudocranial
Slice thickness: 5 mm; increment: 5 mm
Tube current: 80 mA (variable tube current using automated exposure control for dose modulation)
Tube voltage: 140 kV
Pitch: 1.5
Breathing protocol: shallow breathing
If IV contrast is to be administered:
Injection parameters: Volume: 100 cc
Rate: 2 cc/sec
Delay: 70 sec
IV contrast: 300 mg nonionic, iodinated, low-osmolar radiological contrast agent
PET
After body CT is complete, move bed into the PET position
Acquire PET scan of the chest, abdomen and pelvis using
5 min bed positions (BGO crystals); increase to 6 min for heavy patients
3 min bed positions (LSO and GSO crystals); increase up to 5 min for heavy patients, reduce to 2 min for patients weighing <59 kg.
Scan direction: caudocranial
Shallow breathing throughout scan

question tested phasing and timing of the contrast injection in a two-row CT as part of the combined PET/CT tomography. Results may be different in other PET/CT devices using multi-row CT.

Scan Extent

For oncologic evaluations, whole-body coverage is needed. The current standard protocol used for whole-body PET/CT at our institution is performed from the skull base to the upper thighs with a PET/CT scanner with six-slice helical CT (Biograph 6; Siemens Molecular Imaging, Knoxville, Tennessee, U.S.). The patient is positioned first and supine with arms above head supported by positioning aids (e.g., cushions). Positioning aids are used under the knees or ankles as well to increase patient comfort.

Respiration Artifacts

Choosing a method for acquiring the CT scan through the chest requires some consideration of the trade-off between the respiration artifacts created by mismatch between the position of the diaphragm and the expansion of the chest and the relative advantages of having a stationary thorax for the CT images. This method constitutes one of the biggest sources of potential artifacts in the thorax in a

dedicated combined PET/CT scanner is related to differences in breathing patterns when acquiring CT for attenuation purpose and the PET scan. CT scans can be acquired using a standard breathhold technique (e.g., scanning at maximum inspiration), but since PET acquisition requires a more prolonged imaging period during multiple respiratory cycles, misregistration may occur when this protocol is transferred directly from diagnostic CT to combined PET/CT without further adaptation.

Respiratory motion causes the diaphragm to occupy a different position on the image obtained with CT and the image obtained with PET. In fact, PET images record an averaged position of the diaphragm, whereas the faster spiral CT acquisition captures the diaphragm in a single position. This motion may provoke misregistration of organs adjacent to the diaphragm with the appearance of curvilinear cold area or “mushroom” artifacts on PET/CT mostly in the lower thorax, anterior chest wall, and in the posterior internal parts of the liver (12–14). Moreover, since the PET attenuation correction factors are calculated on the basis of complementary CT transmission images (15) misregistration may cause erroneous attenuation correction process leading to potential incorrect diagnosis and erroneous quantification of activity (16). This phenomenon has been observed and quantified in as many as 84% of PET/ CT studies (13).

Acquiring PET data during respiratory gating can reduce the frequency of misalignment in reconstructed PET/CT images (17); unfortunately, in-line PET/CT devices using this capability are still not widely used.

Misalignment in the thorax and abdomen may be minimized using different breathing protocols by performing the CT scan during normal expiration (i.e., the state of respiration at the end of a tidal breathing cycle). Goerres et al. (18) have found that CT acquisition during normal expiration and free breathing provide the best co-registration of whole-body PET/CT data in the thorax in 53% and 27% of patients, respectively.

The applicability of the normal expiration protocol, however, is limited to PET/CT tomographs with very fast CT components or CT protocols that use large table feeds per rotation. Acquiring the CT in normal expiration may not always be feasible in case of very anxious subjects or uncooperative or very sick patients. However, multirow CT beyond two detector rows improves PET/CT co-registration in the absence of gating options and breathhold instructions. Beyer et al. found the fraction of respiration-induced image artifacts in the abdomen on whole-body PET/CT studies to be 60% to 80% for PET/CT with a single-slice CT and 20% to 45% for PET/CT with 16-slice CT (19).

When respiration-induced misalignment persists and appears to introduce artifacts into the corrected PET, non-attenuation-corrected images must be carefully reviewed along with attenuation corrected images. Experienced readers are usually able to recognize respiratory-induced artifacts, which are usually considered not to be diagnostically relevant in most oncologic patients.

Postprocessing: Image Reconstruction

CT reconstructions will vary depending on the body part viewed, but typically in our institution we use a moderately smooth filter for reconstruction of the whole body and a sharper, noisier filter for the chest for viewing the lungs with lung windows to improve visualization of lung detail.

All PET reconstruction is performed at 512×512 . Image reconstruction is ideally performed with an iterative reconstruction algorithm but will vary depending on the PET camera detector size as well as the degree of noise introduced into the PET because of patient body habitus. Both measured CT attenuation-corrected images and non-attenuation-corrected images are provided for viewing.

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4

Clinical PET/CT in the Brain

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INTRODUCTION

While ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) has been used in a myriad of neurologic and psychiatric conditions, most of these are not yet squarely in the clinical arena. It is our intention here to focus on the most clinically documented applications of FDG PET with concomitant computed tomography (CT) findings. Thus, we will focus on the application of PET/CT to dementia, brain tumors, and epilepsy. While brain tumors comprised one of the earliest applications of FDG PET, the use of PET/CT in this setting remains controversial. Many other applications have been described in research settings with sophisticated interventions, either activation studies or drug administration. They are beyond the scope of a practical clinical discussion. Finally, while in-line PET/CT makes the understanding of CT findings essential, in brain imaging, magnetic resonance imaging (MRI) remains standard. For that reason, when appropriate, we have included a brief discussion of MRI findings simply because our patients frequently present with these studies for correlation.

DEMENTIA IMAGING

As our population ages, degenerative dementias become an increasingly important issue in health care. Diagnosis and specific characterization will be required for proper management of these patients and for prescribing appropriate treatments as these treatments are developed. Furthermore, the diagnostician's task will include differentiating mild cognitive impairment (MCI)—by definition an age appropriate memory loss without progression—from neurodegenerative dementias. The most prevalent dementia in the elderly is Alzheimer's disease (AD) affecting 50% to 60% of elderly demented patients. Dementia of the Lewy Body type (DLB) and vascular dementia probably both affect about 15% to 25% of the demented elderly. Frontotemporal dementias are third in terms of prevalence (1–3). Clinical characterization of particular dementias lacks specificity, especially in the early phases of the clinical course, where currently available treatment might be more effective. This differentiation becomes increasingly important as medical treatment becomes available since the administration of anticholinergic medication to patients with AD may result in deterioration (4). And conversely, AD patients,

especially early on, may show improvement in function or at least slowing in deterioration when treated with cholinesterase inhibitors (5). Neurofunctional imaging, specifically F-18 FDG brain PET, and cerebral perfusion single photon emission computed tomography (SPECT) (6,7) are becoming mainstays in the algorithm to improve characterization of these dementias especially in the early phases where clinically differentiation may be problematic.

Alzheimer's Disease

Clinically, memory deficits, visual memory, and naming skills are the most prominent abnormalities in AD (8). Behavioral disturbances and agitation may follow. While psychotic behaviors are less common, depression may be seen in up to 30% of patients (9). Eventually, patients become unable to care for themselves, first in terms of higher level tasks such as managing finances or planning activities; inexorably these disabilities extend to much more basic skills such as eating and personal hygiene. Patients often become bedridden in the later stages (10). Pathologically, the AD brain shows widespread neuronal loss with neurofibrillary tangles consisting of phospho-tau protein (p-tau) and β -amyloid plaque.

Conventional imaging findings on MRI or CT in AD can be subtle at early stages of the disease and confounded by the presence of global cerebral atrophy, which occurs with increasing age. Classically described is mesial temporal lobe atrophy, in particular, of the hippocampus and entorhinal cortex (11–13) (Fig. 1). Volumetric analysis and visual inspection methods have been used to evaluate for atrophy relating to AD (14). One group found the sensitivity of qualitative inspection of thin section MRI to be higher than cerebral perfusion SPECT (80% compared with 60%) and the specificity to be comparable (96% compared with 94%). This finding was using interpretations by expert neuroimagers involved in dementia research in patients with a known clinical diagnosis of AD. The sensitivity was lower for patients with mild AD as well as with less experienced observers (15). In practice, the diagnosis of AD remains difficult to make on conventional MRI and nuclear imaging techniques play an important role.

Characteristic findings associated with AD on FDG PET were identified early in neocortical association area deficits, i.e., temporoparietal regions (16,17) and then later refined to include posterior cingulate and lateral frontal deficits. Typically, PET will show preservation of metabolism in basal ganglia, sensorimotor cortex, occipital cortex, and cerebellum (18). While bilateral temporoparietal deficits are highly suggestive of AD, left-right asymmetry commonly occurs (16,17). The sensitivity and specificity of F-18 FDG PET has been found to vary from 93% to 94% and from 73% to 93% (10,19),

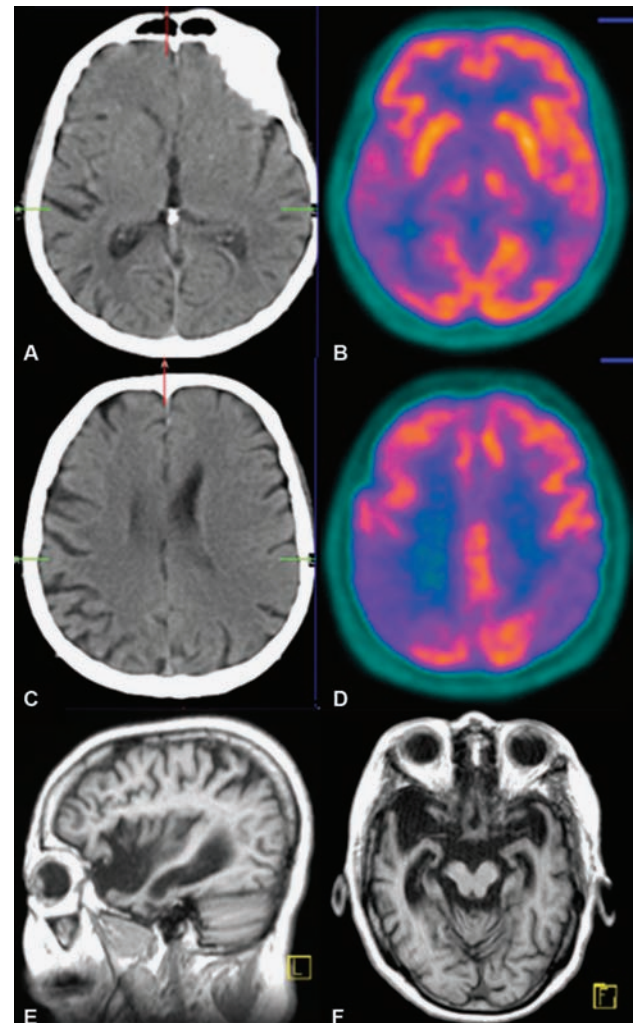


Figure 1 Corresponding CT (A) and FDG PET (B) through the temporal lobes of a patient with Alzheimer's disease show bilaterally diminished, although somewhat asymmetric, temporal lobe uptake as well as preservation of basal ganglia and occipital lobe activity. Corresponding CT (C) and PET (D) images through the parietal lobes at a higher level show the parietal deficits, again asymmetric. Note that the frontal lobes show relatively intact metabolism. The CT images are relatively bland in appearance. Sagittal (E) and transaxial (F) T1-weighted MRI images demonstrate hippocampal atrophy in this patient. *Abbreviations:* CT, computed tomography; FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography; MRI, magnetic resonance imaging.

respectively. Even in mildly affected individuals, the sensitivity may reach as high as 84% with specificity 93%. While our focus here is on FDG metabolic PET imaging, many of the findings apply to cerebral perfusion SPECT as well. However, PET appears to be superior to SPECT for differentiating severe AD from dementias of vascular etiology (7). While SPECT and PET have shown comparable sensitivities for temporal and parietal deficits

of AD, PET may be slightly more sensitive for involvement of other neocortical areas (20) and in early dementia (21). Differentiation of AD from other dementias can be accomplished using FDG PET with high discriminatory ability (17). Differentiation from frontotemporal lobe dementia (FTD) hinges on the decreased uptake in ventromedial cortex in FTD compared with AD and the relative preservation of metabolic activity in the middle temporal gyrus in FTD (22). The distinction between AD and either Lewy body disease or Parkinson's hinges more on the relatively preserved occipital lobe metabolism in AD.

One of the hallmarks of AD is its progressive nature. The identification of a pattern specific to a neurodegenerative dementia such as AD on brain metabolic studies will predict clinical progression in 93% with a specificity of 76% (10). The severity of deficit may also predict clinical cognitive decline (23), especially in those with the apolipoprotein E (apoE)-4 genetic risk. There is a typical pattern of metabolic deficit progression in AD. MCI in early AD may only show deficits in the medial temporal cortex very early on (24), progressing to temporoparietal region and posterior cingulate region. Deficits then extend to the prefrontal cortex and become more profound in the parietal and posterior cingulate cortex (25). Moreover, as the dementia progresses, typical shifts in the pattern of deficits will be observed in AD with involvement of the frontal association cortex, but with the preservation of primary motor and sensory cortex (10,26).

In patients with early MCI there is much interest in identifying those who will progress to frank AD as compared with those who will remain stable or even normalize in their cognitive function. Although elevated cerebrospinal fluid (CSF) levels of p-tau, the major component of the neurofibrillary tangles associated with AD, have been associated with the metabolic pattern of AD on FDG PET in patients with MCI likely to progress (27), in general, neuropsychologic testing, e.g., mini-mental status examination scores, or biochemical markers have not proved a reliable differentiator (23). In patients with MCI, severe metabolic deficits carry a much higher risk of deterioration than mild or moderate deficits (28) (Fig. 2). Even in apoE-4 negative but mildly impaired individuals, parietal association cortex deficits (29), specifically the posterior cingulate, inferior parietal, and lateral temporal regions (25,30,31) have been shown to differentiate those who will progress to AD. While some have identified left-sided deficits as more predictive (30), others have found right inferior parietal cortical deficits to be the differentiator between MCI and conversion to AD (25,29,31). The more profound right-sided deficits in these early patients may explain the relatively mild cognitive manifestations where profound pathologic and metabolic changes are already occurring. One study has described deficits confined to the dorsolateral frontal cortex in

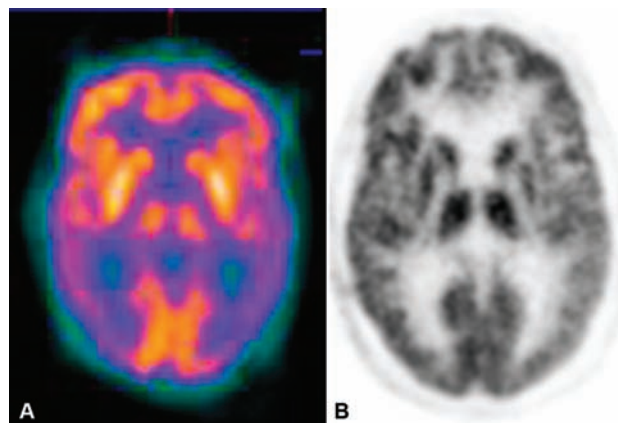


Figure 2 Transaxial PET image (A) shows pronounced bilateral temporoparietal deficits in a patient with only minimal cognitive impairment but with a family history of Alzheimer's disease. This patient went on to progress to frank dementia. Transaxial FDG PET image (B) shows minimal deficit in the left temporal lobe in a patient with stable mild cognitive impairment that did not interfere with daily activities. *Abbreviations:* PET, positron emission tomography; FDG, ^{18}F -fluoro-2-deoxy-D-glucose.

subjects with MCI in contrast to far more extensive and bilateral parietal and temporal lobe deficits (32). Most of these studies rely on quantitative PET and statistical parametric mapping rather than qualitative visual assessment. Still others have focused on medial temporal metabolism using higher resolution PET scanners and sophisticated MRI mapping (24). Although there are reductions in glucose uptake in the hippocampus in patients with MCI (approximately 10% below normals), these are significantly greater in patients with AD (about 33% below normals). This has been validated both with quantitative PET and combined with statistical parametric mapping. However, qualitative visual analysis of the medial temporal cortex also provides a robust and sensitive means of differentiating AD from MCI (sensitivity 100%, specificity 77%) (24).

Advanced MRI techniques, including spectroscopy and perfusion (33), have been used in research settings. Decreased *N*-acetyl aspartate (NAA) and increased myoinositol have been reported in various cerebral locations in patients with AD (34). While some groups have found MR spectroscopy (MRS) to be useful in differentiating between AD from other dementing disorders including MCI, vascular dementia, and depression, currently none of the metabolic markers evaluated are specific (35). There is an ongoing interest in the serial evaluation of cerebral metabolites in patients with progressive dementing diseases. In particular, there is an interest in evaluating patients with MCI and determining if there are findings or markers which can predict cognitive decline (36–39). High-field MRS in the evaluation of dementia is also

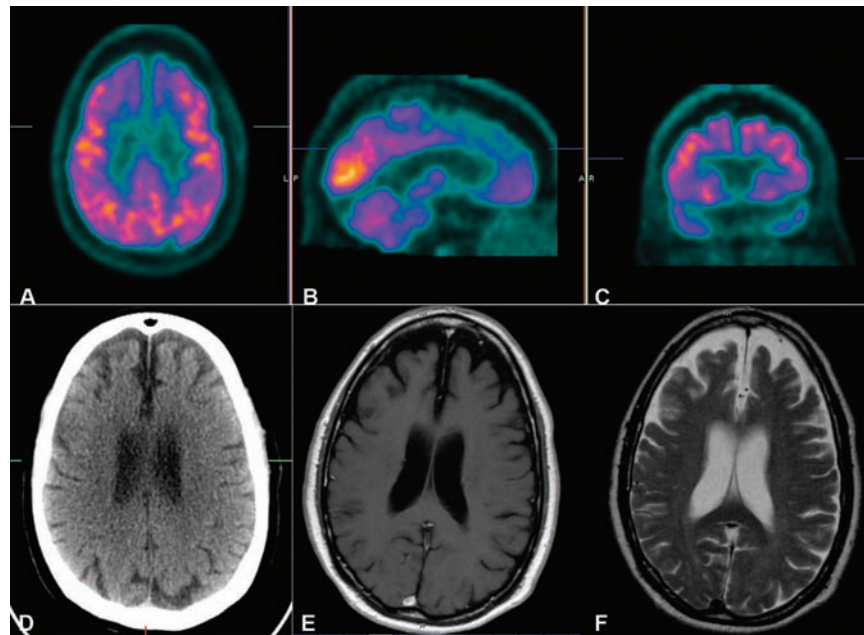


Figure 3 Transaxial (A), sagittal (B), and coronal (C) FDG PET images in a patient whose family noted apathy and decreasing social engagement with her family members. Note the decreased metabolic activity in the frontal lobes and temporal lobes typical of frontotemporal dementia. Corresponding transaxial CT image (D) and T1-weighted (E) and T2-weighted (F) MRI demonstrates frontal lobe atrophy out of proportion to the parietal lobes. *Abbreviations:* FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

currently underway (40) and, in the future, may provide additional information.

Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration includes a spectrum of clinical entities with some pathologic overlap: Pick's disease, progressive supranuclear palsy or FTD/MND, semantic dementia, and progressive primary aphasia. Semantic dementia and progressive primary aphasia are considered separate entities as the pathologic and clinical characterization of these entities improve (41). Memory deficits are less prominent in FTD as compared with Alzheimer's dementia, but early alterations in behavior, extending even to the sociopathic level, and changes in personality such as apathy, passivity, hyper oral behaviors, loss of empathy, and emotion may be observed (42,43). FTD, multi-infarct dementia, and depression are clinically difficult to distinguish from AD in many instances. In fact, depression may be the first manifestation of FTD. Pathologically, FTD is characterized by the presence of tau bodies and has been associated with chromosome 17 abnormalities. Neurofunctional imaging has become part of the criteria for diagnosis because metabolic and cerebral perfusion studies show such specificity (44). MR spectroscopy abnormalities in a large spatial area have been described in FTD. As in AD, diminished NAA as well as decreased NAA/Cr (*N*-acetyl aspartate/

creatine) and NAA/Cho (*N*-acetyl aspartate/choline) ratios are seen but occur in a different distribution (45,46).

Early on patients show deficits in the frontal lobes on neurofunctional imaging (47–49) (Fig. 3), but as the dementia progresses there is more involvement of the orbitofrontal cortex, the caudate, the insula, and the thalamus (48,50). Also, as the dementia progresses, FDG PET shows the parietal and anterior temporal lobes to be more affected (48,51). There is pathologic evidence for involvement of the frontal lobe.

Not surprisingly, MRI shows morphologic evidence of frontal lobe atrophy in patients with FTD (Fig. 3) (52). This is seen with greater reliability in patients with more advanced FTD who typically demonstrate selective atrophy of the frontal and temporal regions with relative sparing of the parietal and occipital brain on CT or MRI. Again, this finding can be difficult to perceive unless already quite advanced. However, it remains to be seen how much of the subcortical deficit is because of deafferentation or neuronal degeneration. It has been hypothesized that diffusion tensor MRI may be able to differentiate the two (48). As FTD progresses, temporal and parietal metabolic deficits become more prominent on neurofunctional imaging as well (48). This prominence is seen on cerebral perfusion SPECT imaging also (53).

Progressive supranuclear palsy (PSP) is characterized clinically by supranuclear gaze palsy, Parkinsonism, postural instability, dysarthria, rigidity, and pyramidal signs

(54). PSP may compose about 18% of patients with FTD (55). On functional neuroimaging, similar to FTD, PSP is characterized by subcorticofrontal deficits with significant deficits in the frontal lobes bilaterally, the basal ganglia, and thalamus (55). The frontal cortex deficit correlates with pathologic findings (56). Further differentiation between FTD and progressive supranuclear palsy can be attained with statistical parametric mapping of FDG PET (54). Compared with healthy aged matched individuals, subjects with PSP are found to have statistically significant deficits in precentral, dorsolateral premotor, left ventrolateral premotor, left dorsolateral prefrontal, left frontopolar, and left anterior cingulate regions. Statistically, no significant difference is seen between FTD and PSP in the frontal cortex, but PSP shows greater occipital cortex (bilateral) and left cingulate gyrus (BA19) deficits. Some have suggested that cortical involvement in PSP is confined to the frontal lobes (55); yet subcortical structures appear to be affected in PSP, including midbrain tegmentum, bilateral putamen, and left medial dorsal nucleus of the thalamus. Pathologically, only the midbrain tegmentum is usually observed to be affected (57), suggesting that other subcortical structures are secondarily affected because of reduced input (54). How easily this translates to qualitative evaluation of neurofunctional images is uncertain. In general, more profound deficits are seen in patients with FTD compared with PSP in frontal cortex with extension into the anterior temporal lobes in FTD (55). More symmetrical deficits are seen in FTD, especially early on (48). The striatal deficits observed in FTD compared with PSP occur mostly in the putamen and have been ascribed to deafferentation from the frontal cortex rather than primary pathologic involvement (49). They appear to be more prominent as the severity progresses (58).

Deficits in primary progressive aphasia are predominantly left sided and frontal (59,60), both on functional imaging and pathologically.

Semantic dementia has been associated with metabolic deficits and atrophy on MRI in the anterior temporal regions (52,61–64). Comparison with FTD subjects has shown a temporal lobe deficit as opposed to a frontal deficit (49) with specific deficits in the entire left temporal lobe and inferior right temporal pole and not in the frontal lobes. Also, thalamic deficits, possibly, on the basis of deafferentation have been observed (49).

Lewy Body Disease

Diffuse Lewy body disease (DLB) shows neuronal loss with Lewy bodies and α -synuclein-containing Lewy body neuritis on histopathology. This entity remains a diagnostic challenge. On neuropsychologic testing, DLB patients will tend to show greater deficits in verbal fluency,

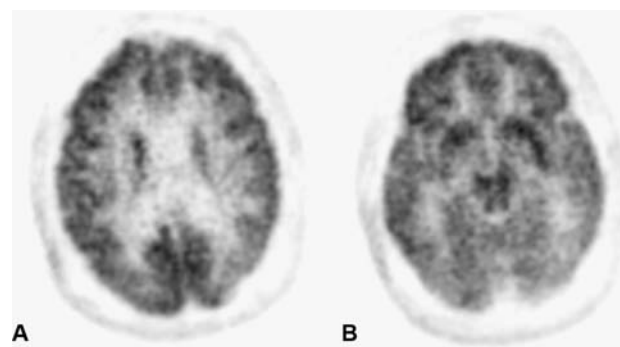


Figure 4 Transaxial FDG PET image through the parietal lobes (A) demonstrates decreased metabolic activity in the left occipital cortex. The slice through the temporal lobes (B) shows diminished bilateral temporoparietal deficits. The CT scan was unremarkable in this patient with dementia secondary to diffuse Lewy body disease. *Abbreviations:* FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography, CT, computed tomography.

nonmotor visuospatial discrimination, attention, and fine motor/psychomotor speed (8). It is in this setting that F-18 FDG PET imaging offers particular utility. While DLB and AD both show PET deficits in temporoparietal, lateral temporal, and prefrontal cortex, DLB patients are likely to show occipital cortex deficits as well (Fig. 4) (8). The specificity (80%) of hypoperfusion in the occipital lobes for differentiating DLB from AD has been shown repeatedly in metabolic (65,66) and cerebral perfusion SPECT studies (67).

Parkinson's Disease

FDG PET in patients with Parkinson's disease typically shows decreased parieto-occipital metabolism. This decreased metabolism may be more pronounced in patients with autonomic dysfunction, i.e., where orthostatic or postprandial hypotension is a prominent manifestation (68) or in patients with accompanying dementia (65,69). Still others have suggested that parieto-occipital deficits in clinically nondemented patients may accompany more discrete cognitive deficits in short-term memory and visuospatial abilities (70) and possibly presages the onset of the dementia that may occur in 10% to 40% of Parkinson's disease patients. Even in early onset disease, primary visual motor cortical deficits occur possibly because of decreased input from the nigrostriatal structures, but should become more severe and more symmetric as the disease progresses (71). These cortical glucometabolic deficits are accompanied by 18F-DOPA kinetic (Ki) deficits in the putamen and caudate obtained from dynamically acquired and modeled studies (72).

However, ^{18}F FDG studies do not typically demonstrate subcortical deficits in these patients (72).

Parkinson's disease and atypical Parkinsonian disorders frequently have no conventional MRI or CT imaging findings early in the course of these diseases. Later on, as the diseases progress, different patterns of atrophy have been described and have been used by some to differentiate between these entities. In one study, putaminal and vermian atrophy was found to be more common in patients with multisystem atrophy, whereas cortical and midbrain atrophy was found to be more common in patients with progressive supranuclear palsy and corticobasal degeneration (73). The main role of structural imaging, however, is to exclude other intracranial pathologies, in particular mass lesions that may lead to extrapyramidal symptoms mimicking Parkinson's disease and atypical Parkinsonian disorders. In general, MRI is preferred over CT for this.

Patients with Parkinson's disease have been shown pathologically to have an abnormal accumulation of iron and a corresponding loss of neurons in the substantia nigra pars compacta (74). This interrelation can be observed on MRI as an increase in susceptibility or a decrease in signal intensity in this region. This finding is difficult to appreciate qualitatively, but quantitative studies have shown decreased signal as well as decreased volume in the substantia nigra in patients with Parkinson's disease compared with normal controls. This finding has been correlated with poor clinical score (75).

Conventional MRI techniques have a limited role in the evaluation of Parkinson's disease, atypical Parkinsonian disorders, and Parkinson-related dementia, but can, however, aid in presurgical planning for the placement of deep brain stimulators (76,77) (Fig. 5). Efforts at using other advanced MRI techniques include studies involving

diffusion-weighted imaging (78,79), proton spectroscopy (80), functional MRI (81), and magnetization transfer ratio measures (82,83). A recent study incorporating ^{31}P -MRS showed impaired oxidative metabolism in temporoparietal cortex (70). The clinical applications of these advanced techniques are not yet certain.

Cerebrovascular Disease

Cerebrovascular disease is a common cause of dementia in the elderly, reportedly occurring in about 2% to 16% of the elderly demented at autopsy. It may occur in concert with Alzheimer's disease in 4% to 18 % of patients (84). The spectrum of cerebrovascular disease ranges from frank transcortical infarcts to small lacunar infarcts to leukoariosis. These changes can be appreciated on conventional cross-sectional imaging and are usually more evident on MRI compared with CT. Regions of transcortical infarction typically reside within a single vascular distribution and, in the chronic phase, result in gliosis and volume loss (Fig. 6). Small lacunar infarcts are frequently seen in conjunction with changes consistent with leukoariosis. Lacunar infarcts are well-circumscribed, subcentimeter regions that are similar in CT attenuation and MRI signal intensity to fluid. These are commonly seen within the deep gray matter as well as the white matter. Leukoariosis manifests as abnormal hypodensity on CT or corresponding areas of signal abnormality on MRI usually affecting periventricular and subcortical white matter.

Leukoariosis is a common finding with a positive association with age, smoking, cardiovascular disease, and hypertension (Fig. 7) (85). It is generally believed to be a result of microvascular ischemia. Some investigators have shown that the severity of leukoariosis reflects the degree of cognitive decline in elderly patients (86,87), though

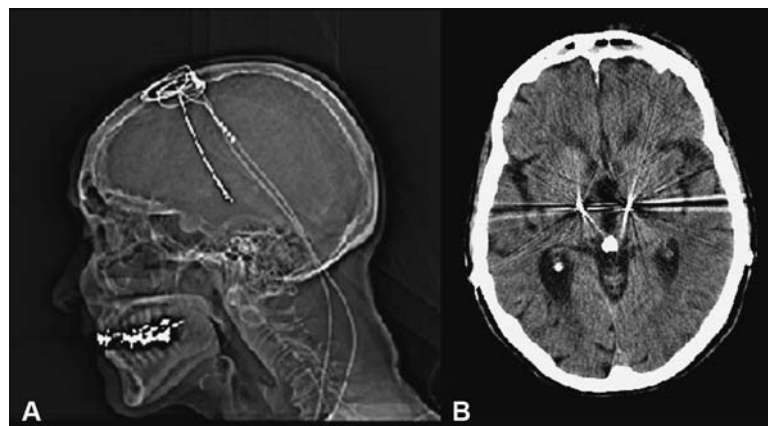


Figure 5 Lateral CT scout image (A) and noncontrast transaxial CT (B) images through the level of the thalamus and midbrain demonstrate bilateral brain stimulators in the subthalamic region in this patient with a clinical diagnosis of Parkinson's disease. *Abbreviation:* CT, computed tomography.

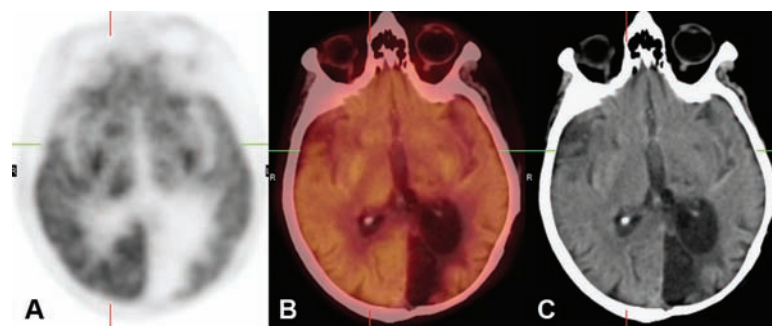


Figure 6 Transaxial FDG PET image (A) shows a profound metabolic deficit corresponding on the fused PET/CT (B) and the CT (C) image to loss of occipital brain volume, gliosis, and accompanying enlargement of the left occipital horn at the site of a previous left posterior cerebral artery infarction. Also note the presence of a multiple left-sided lacunar infarcts in the thalamus and white matter adjacent to the basal ganglia. *Abbreviations:* FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography; CT, computed tomography.

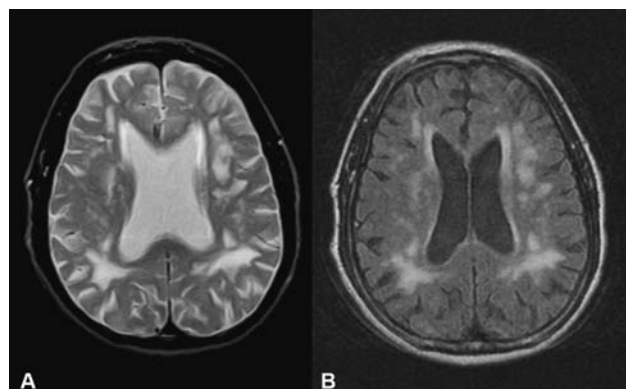


Figure 7 82-year-old patient with dementia has areas of abnormal white matter on MRI, seen here as regions of hyperintensity on axial T2 weighted (A) and FLAIR (B) images. *Abbreviations:* MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery.

others have found no correlation between severity of white matter changes as determined by MRI and cognitive or behavioral assessments (88). In practice, the presence of CT or MRI changes compatible with microvascular ischemic disease is frequently seen, not entirely specific, and not predictive of a patient's cognitive function.

Embollic disease and hemodynamic mechanisms can also contribute to vascular dementia (89). In one autopsy series, about a third of vascular dementias were of the small multi-infarct type and two-thirds because of subcortical infarcts (84). Large vessel disease is a much less common cause of dementia than micro and subcortical infarcts (90). Differentiating vascular dementia from AD or even identifying mixed AD and vascular dementia is difficult on both clinical testing and FDG PET (91). The amount of brain involved in both entities is similar for a similar level of cognitive deficit (92). Furthermore, patients with vascular dementia tend to have parietal lobe deficits on metabolic and blood flow

imaging (93,94). While some have observed metabolic deficits in the temporal lobes in both entities, others suggest that the temporal lobes may be somewhat spared in vascular dementia compared with AD. Metabolic deficits on functional imaging like FDG PET may represent direct loss of functioning tissue or remote deafferentation effects, e.g., diaschisis. Structural or morphologic imaging like MRI or CT has an important role to play in identifying these patients (84). Abnormalities of vascular etiology affecting multiple vascular territories are suggestive of embolic phenomenon. In addition, the involvement of limbic structures, e.g., the hippocampus, frontal-subcortical circuits can predict cognitive deficits in vascular dementia (89).

A subdivision of vascular dementia has been suggested, i.e., cortical vascular dementias which encompass large vessel disease and embolic disease and are typically abrupt in onset. The so-called "strategic infarct dementia" encompasses patients with small lesions in very specific and sensitive sites such as the hippocampus or the thalamus and may have either small vessel etiology identified by lacunar infarcts or more diffuse white matter disease. They may also have a larger vessel etiology and show the typical changes on CT or MRI of arterial watershed infarct. Finally, subcortical dementias include what is typically known as Binswanger's disease. Binswanger's disease is associated with hypertension, and patients frequently demonstrate white matter and subcortical lacunae as well as regions of transcortical infarcts in the setting of more diffuse white matter disease. Again, CT and MRI findings are nonspecific and include patchy or diffuse periventricular areas of decreased attenuation or signal abnormality, which may extend into the centrum semiovale and the presence of scattered lacunae and possibly cortical regions of ischemic stroke. Atrophy, especially ventricular enlargement, can be seen as well (95). In limited evidence from trials of propentofylline, a phosphodiesterase inhibitor that limits reuptake of adenosine in the brain, FDG PET has

shown improvement in motor cortex metabolism over a relatively short period of three months in treated patients compared with controls. This was associated with improvements in visual information processing (96). Although this drug remains under investigation, the study suggests that FDG PET could be used to monitor effects of drug treatments in vascular dementia.

A prototype of a dementia of vascular etiology is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is associated with a mutation on the *Notch 3* gene. These patients are usually affected between the ages of 30 and 50 and present with stroke-like symptoms and cognitive and behavioral changes with approximately 28% of patients developing dementia (97). Smooth muscle deficits in the walls of small and medium-sized arteries lead to thrombosis and multiple lacunae usually involving frontal lobe white matter and subcortical gray matter. On T2-weighted MRI, white matter hyperintensities in a periventricular distribution are typical. The changes may resemble multiple sclerosis changes or microvascular ischemic disease and involvement of the internal capsule is common (98). Small infarcts (single or multiple) are frequently evident on T1-weighted MRI and CT, usually in the basal ganglia, white matter, or brainstem. CADASIL typically affects the subcortical U-fibers. A positive family history, the presence of white matter abnormalities in a non-hypertensive patient, and selective early involvement of the anterior temporal lobe and external capsule may help to differentiate CADASIL from other entities (99) (Fig. 8).

Both cerebral blood flow and FDG metabolic PET studies show scattered deficits secondary to frank infarcts (100) involving subcortical but not cortical structures (101). However, secondary, deafferentation deficits will be seen in the frontal, temporal, and parietal cortices, with relative sparing of the occipital cortex (101). These deficits are often asymmetric and may be accompanied by cerebellar diaschisis. These findings may be indistinguishable from patients with the nonfamilial subcortical vascular dementias. Similar changes may be seen in patients with primary antiphospholipid antibody syndrome, which is associated with progressive dementia and also in patients with systemic lupus erythematosus (102).

TUMOR IMAGING

Metabolic FDG imaging showed its earliest promise in the evaluation of primary brain tumors (103,104), but the substantial uptake of FDG by normal brain and the less than perfect specificity of FDG for brain tumors have since proved FDG to be problematic in the metabolic evaluation of central nervous system (CNS) neoplasm. In fact, except for high grade gliomas and a few low grade tumors such as pilocytic astrocytomas, choroid plexus papillomas, and

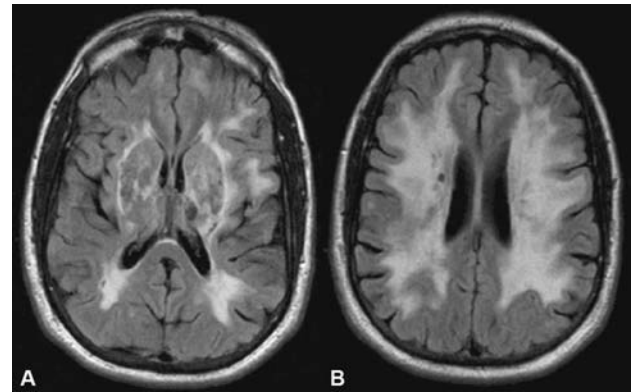


Figure 8 Axial FLAIR MRI images through the basal ganglia (A) and at the level of the lateral ventricles (B) in this 44-year-old non-hypertensive man with a change in mental status, demonstrate confluent areas of signal abnormality in the white matter, and focal lacunar infarcts in the pons and left thalamus. Subcortical U-fibers are involved, as are the external capsules and anterior temporal white matter. In conjunction with a positive family history and lack of hypertension, these latter findings are felt to help to differentiate CADASIL from microvascular ischemic and demyelinating diseases. *Abbreviations:* FLAIR, fluid attenuation inversion recovery; MRI, magnetic resonance imaging; CADASIL, cerebral autosomal dominant arteriopathy with subacute infarcts and leukoencephalopathy.

pleomorphic xanthoastrocytomas (Fig. 9) (105–108), most types of primary brain tumors are likely to show less intense uptake than normal gray matter (109). The literature is equivocal on the utility of FDG for tumor grading and for assessing recurrence; however, thus far FDG remains the only approved PET tracer for CNS tumor imaging. Better PET radiotracers that reflect either amino acid uptake or thymidine kinase activity may soon be more widely available and appear promising (110–114). These radiotracers appear to offer advantages in terms of sensitivity and probably specificity. While C-11 methionine (MET) is unlikely to become widely available due to its short physical half-life, F-18 fluoro-L-thymidine (FLT) and F-18 fluoro-L-ethyl-tyrosine (FET) may receive approval and come into broader clinical use. The utility of studies using these newer radiotracers is reviewed here, perhaps optimistically, but also because the clinical studies reported so far are quite compelling.

Conventional Anatomic Imaging of Brain Tumors

Anatomic imaging modalities including CT and MRI remain the method of choice for imaging brain tumors. CT examination is sometimes performed as a screening modality and is also useful in the immediate postoperative period. Contrast-enhanced CT is much more sensitive than a noncontrast study for intracranial neoplasm such as

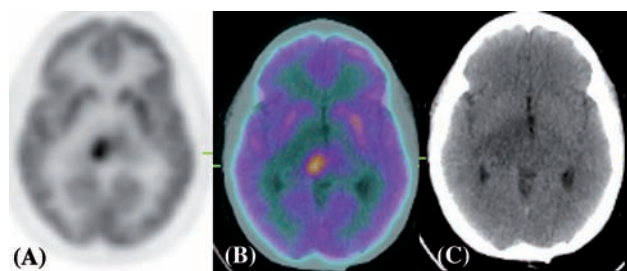


Figure 9 Transaxial FDG PET (A), fused PET/CT (B), and corresponding CT slice image (C) show intense uptake at the site of this patient's pilocytic astrocytoma with slightly decreased density and mass effect on the noncontrast CT. Although this is not considered a high-grade malignancy, pilocytic astrocytomas do demonstrate intensely increased metabolic activity. *Abbreviations:* FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography; CT, computed tomography.

metastatic lesions, high-grade gliomas, and solid extra-axial masses (including meningioma, ependymoma, and choroid plexus tumors), all of which frequently have areas of avid enhancement. Low-grade CNS tumors may not enhance. In evaluating the contrast-enhanced study, care must be taken to compare to a noncontrast study to confirm that hyperdense areas on the postcontrast examination do indeed represent areas of enhancement rather than areas of hemorrhage or even fine calcification.

Noncontrast CT, as is performed routinely with PET as part of a PET/CT, is not a sensitive test for intracranial neoplasm because of differences in technique and lack of contrast administration. Noncontrast CT will only show gross abnormalities such as large tumors and substantial amounts of edema or mass effect. Edema is seen on CT as regions of hypodensity in the white matter associated with regional mass effect (Fig. 10). Mass effect is seen as effacement of the sulci, or when severe, shift of the midline or effacement of the basal cisterns. When severe, this latter finding can indicate uncal or transtentorial herniation and is a surgical emergency. Determination of the location of a mass as extra-axial or intra-axial can be difficult on non-contrast CT. If the sulci or vessels are visualized as being displaced from the inner table of the skull, this is consistent with an extra-axial lesion. Contrast enhancement frequently helps with this delineation. Also, sagittal images, which are available more often with MRI, may help show the relationship of a mass to the meninges (Fig. 11).

Cystic regions of tumors can be identified on both contrast-enhanced and noncontrast CT examinations. Certain tumors such as juvenile pilocytic astrocytomas form cysts more frequently, although occasionally tumor cysts and regions of cystic necrosis are difficult to differentiate. Cysts may not always have the same attenuation as CSF, as they can contain hemorrhagic products or proteinaceous fluid. Noncontrast CT does, however, demonstrate

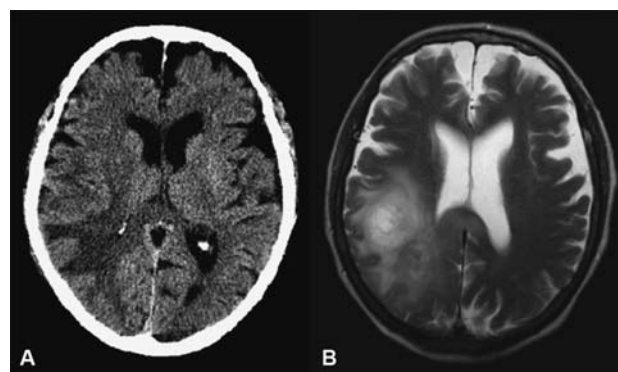


Figure 10 Noncontrast CT (A) performed to evaluate for stroke in an elderly woman who presented with left hemiparesis shows the mass effect and vasogenic edema surrounding a tumor involving right parietal and occipital white matter. On T2-weighted MRI (B) the edema and underlying lesion are seen to better advantage as signal abnormality. Biopsy showed a glioblastoma multiforme. *Abbreviations:* CT, computed tomography; MRI, magnetic resonance imaging.

calcifications well, which are frequently difficult to visualize on MRI (Fig. 12). In conjunction with MRI, this can aid in the differential diagnosis. CT is also useful in examining the calvarium for bone involvement or bone disease (Fig. 13).

Gadolinium-enhanced MRI is the gold standard for anatomic brain tumor imaging. It provides exquisite anatomic delineation of intracranial masses, information on adjacent structures and mass effect, and a means for accurate serial comparison for the evaluation of disease progression. Contrast-enhanced MRI is currently used to image all intracranial masses including malignant and benign lesions, primary and metastatic tumors, and high- and low-grade primary neoplasms, and it can also

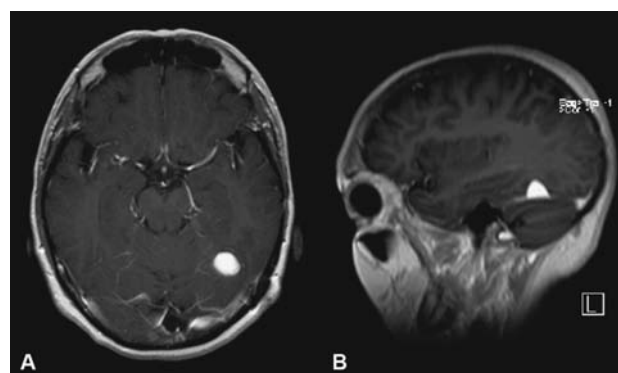


Figure 11 Transaxial images (A) through this extra-axial lesion do not show the location of the lesion definitively. Sagittal post contrast T1-weighted images (B) show the broad attachment to the tentorial dura and the extra-axial location of this meningioma.

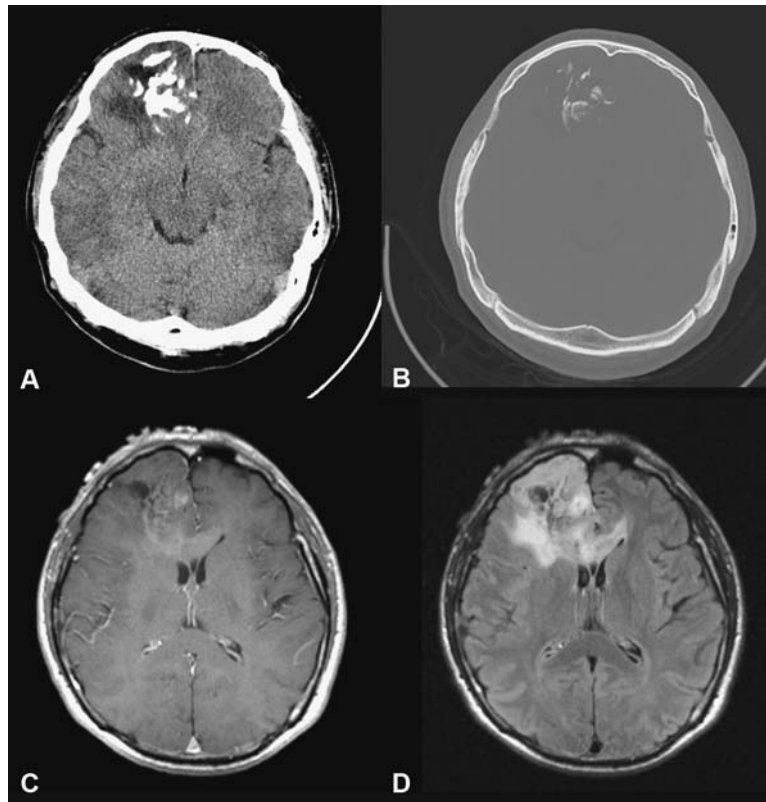


Figure 12 Noncontrast CT performed on a 44-year-old man with a history of oligodendroglioma shows calcifications typical of this tumor on both brain windows (A) and bone windows (B). Postcontrast T1-weighted MRI (C) and FLAIR images (D) show susceptibility artifact secondary to the calcifications; the edema and tumor are better demonstrated compared with CT. *Abbreviations:* CT, computed tomography; MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery.

delineate multiplicity and extent of lesions. Edema and mass effect are well demonstrated with vasogenic edema seen as an area of T2 hyperintensity in white matter associated with mass effect. Enhancement corresponds to extra-axial lesions, parenchymal metastatic lesions, or in the case of primary glial neoplasms, a breakdown of the

blood-brain barrier. MRI venography and MR angiography add useful preoperative information such as the relationship of the mass to major vessels as well as insight into the arterial supply and venous drainage. An in depth discussion on the MRI characteristics of intracranial neoplasm is beyond the scope and aim of this chapter.

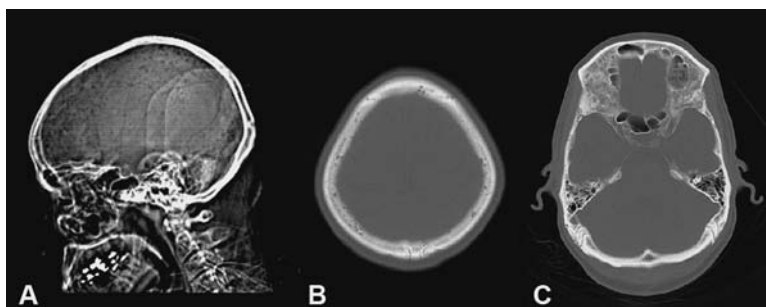


Figure 13 60-year-old man with multiple myeloma and skull involvement. Multiple calvarial lucencies in this patient are well demonstrated on sagittal CT scout image (A) as well as axial images on bone windows (B and C). *Abbreviation:* CT, computed tomography.

While MRI plays an undeniably important role in identifying the presence and extent of tumor, the mapping of either FDG PET, FLT, FET, or C-11 MET PET onto brain MRI has shown that gadolinium-enhanced MRI frequently underestimates the extent of tumoral disease, particularly in the case of infiltrating neoplasms (111,113,115,116). Additional information can be provided by metabolic images and, when used in combination with conventional MRI and MRS (117), may prove to be a powerful tool in the assessment of CNS neoplasms including tumor grading, targeting biopsy sites for greater diagnostic yield, evaluation of low grade tumors for malignant degeneration, as well as the definition and assessment of surgical margins.

Grading and Detection of Primary Brain Tumors

FDG uptake in brain tumors is independent of the integrity of the blood brain barrier and is unrelated to blood flow, making this a unique method to evaluate metabolic function *in vivo*. High-grade tumors will show FDG uptake either more intense or equal in intensity to normal gray matter (114). The correlation between FDG uptake and histologic grade in adult gliomas has been well established (109,118–121) and appears to hold true in pediatric brain tumors as well (122); yet FDG lacks sensitivity in practice because the intensity may not exceed that of normal brain (123). Nonetheless, since brain tumors are often heterogeneous in histology, FDG PET uptake can be used successfully to localize the most anaplastic portion of a primary brain tumor for biopsy (124,125). In pediatric tumors, heterogeneity on FDG PET may be a marker distinguishing malignant tumors from the more benign tumors like juvenile pilocytic astrocytomas that may also show intense FDG uptake (122). For medulloblastomas, greater FDG uptake predicts a shorter overall survival (126).

FDG PET activity has been shown to accumulate in more invasive meningiomas, distinguishing high-grade from low-grade tumors, as well as metastatic meningioma (127,128). The presence of FDG uptake does not, however, predict recurrence (128). Radiolabeled amino acid accumulation has also been shown to correlate with proliferative activity in meningiomas (129).

Other PET tracers including C-11 MET, F-18 FET, and F-18 FLT may show greater tumor to normal contrast and greater sensitivity including in high-grade tumors compared with FDG (110,113,116). Where FDG PET fails, e.g., in low-grade tumors, radiolabeled amino acids are often far more positive (130). However, while uptake of these newer radiotracers appears to be related to glial tumor grade, this information may be of

limited use in actually predicting histologic grade since there is a continuum of degree of uptake (115). Kinetic analysis of FET uptake, while technically more challenging, may prove to be more helpful in tumor grading (110). One study has shown that FET uptake in low-grade tumors tends to increase over time while in high-grade tumors, FET uptake tends to decrease (110). The uptake of FET by brain tumors appears to reflect increased amino acid transport, not protein synthesis (131). Furthermore, its specificity exceeds that of C-11 MET and FDG (132,133).

FET has been used in combination with MRI and MRS (NAA/Cho ratios) to improve diagnostic yield in targeted biopsies. In one head to head comparison, MRS showed 100% sensitivity and 81% specificity, while FET had 88% sensitivity and 88% specificity. Both were more sensitive and specific than gadolinium-enhanced T1-weighted MR images alone and when FET PET was used in combination with MRS, additional information was provided (115). In fact, the negative predictive value of the combination of FET PET and MRS has been reported as 100%, with a positive predictive value of 97% (131). Both MRS and FET uptake can show tumoral disease beyond the confines of Gadolinium enhancement seen on conventional MR images (111,115).

FLT shows a lower sensitivity (73–79%) for glial tumors than radiolabeled amino acids, especially in low-grade astrocytomas (113,114). The distribution of FLT may differ from that of either gadolinium enhancement or C-11 MET uptake (113). As with FDG, FLT uptake tends to increase with histologic grade. It is believed that uptake of FLT in brain tumors may require a breakdown of the blood brain barrier and reflects increased transport of nucleosides as well as increased thymidine kinase activity (109,113). FLT uptake is, however, not specific and false positives have been reported in multiple sclerosis, radiation necrosis, and subacute infarction (114).

Both amino acid tracer uptake and FDG uptake have prognostic implications for patients (111). Because of biopsy sampling error, FDG uptake-based prediction exceeds the accuracy of histologic grading both in gliomas and meningiomas (134). FDG may also be useful in predicting the behavior of low-grade gliomas and benign tumors such as vestibular schwannomas (135).

Treatment Planning

For planning both surgical resection and radiation therapy, the additional information provided by PET studies over MR or CT may assure a more complete resection or improve the efficacy of external beam radiation. While

FDG can show additional extent of tumor compared with coregistered conventional MRI in some instances, its potential is lessened because normal gray matter uptake may be so similar (136). It has been suggested that since intensity of uptake on FDG PET corresponds to tumor grade, an intensity-modulated radiation therapy (IMRT) boost to those areas might be warranted (119).

Radiation Treatment Planning

C-11 MET, although not available without an in-house cyclotron, has shown greater tumoral volume than Gadolinium-enhanced MR images or contrast-enhanced CT both in the setting of meningioma (137), where contrast enhancement is the standard for identifying tumor extent, and in glioma (138–141) even in the case of low-grade gliomas (142). In 67% of one series of patients with glioma, the extent of C-11 MET uptake exceeded the area of enhancement on either MRI or CT but was comparable in the remaining tumors (143). Other investigators have found additional information on amino acid PET over MRI in only about a third of cases with another third showing a smaller extent of uptake compared with the degree of contrast enhancement (144,145). Another comparison of T1-weighted, gadolinium-enhanced MRI with amino acid PET showed a wider region of amino acid uptake than enhancement in 79%. In comparison to T2-weighted images, amino acid PET uptake may extend beyond areas of hyperintensity, but the reverse can be true as well (129,145). This is not surprising as T2 prolongation can occur in a variety of pathologic settings including infiltrative tumoral disease and vasogenic edema. Metabolic PET imaging may help to define these differences. Encouragingly, FET, an amino acid labeled with the longer lived F-18, has shown very similar distribution to C-11 MET and should offer the same advantages in determining treatment volumes (146). These advantages are expected to lead to more effective radiation therapy treatment plans where tumor extending beyond the region delineated by enhancement will be included in the field.

Surgical Planning

Similarly, as imaging becomes a more integral part of surgical planning, studies using both FDG PET and amino acid PET coregistered with MRI may offer additional information and make possible more complete resections. Most recurrences of resected brain tumors occur within 2 cm of the surgical margin (147,148). More complete resections have been shown to improve prognosis in low-grade gliomas for adults and to a lesser extent in ana-

plastic astrocytomas and glioblastoma multiforme (130). Contrast-enhanced MRI, T2-weighted and FLAIR (fluid attenuation inversion recovery) MRI are standard for treatment planning in glioma. Yet in one series, FDG and amino acid PET added information to MRI in 80% of the 103 patients (130). In that study for high grade gliomas, FDG PET led to more focused resections of tumor compared to the volume dictated by MR. Amino acid PET increased the volume for resection or decreased it in both high grade and low grade gliomas relative to T2-weighted and FLAIR MRI. In another study of pediatric brain tumors, a study of FDG PET coregistered with MRI frequently showed abnormal FDG uptake beyond the confines of the MRI abnormality and also identified additional areas of heterogeneity within the tumor (122).

After surgical resection, amino acid-based PET may be helpful in indicating the completeness of resection (111,116). This is particularly helpful in the treatment of pediatric brain tumors, where complete resection is a key prognostic factor (116,130). Both FDG and C-11 MET have been used to identify residual tumor when MRI shows abnormality at the margin of resection. From this finding a decision about second look surgery can be made, especially with ependymomas, craniopharyngiomas, medulloblastomas, and gliomas in children (116). Depending on location of residual tumor, alternative therapy with radiosurgery may be indicated.

Brain Metastases

The utility of scanning the brain in patients with known primaries has received a great deal of attention and resulted in a moderate amount of controversy. Nonetheless, the sensitivity of FDG PET for brain metastases is low. Only 61% in a group of 40 patients with diverse primary tumors showed increased uptake (149). In that group the lack of sensitivity was attributed to size (Fig. 14). MRI far out-performed FDG PET. The detection rate of cerebral metastases in a large number of whole-body PET scans done for general staging has been low. In one series of over 1000 patients only 0.4% showed cerebral metastases on FDG PET (150). Nonetheless, some metastases may show as increased uptake (Fig. 15). In a reverse strategy, whole-body PET in patients who presented with brain tumors was helpful in distinguishing between primary brain tumors and cerebral metastases by virtue of excluding abnormal extracerebral uptake with a specificity of 94%. Whole-body PET has also been useful in identifying the extracerebral primary tumor in patients who present with brain metastases with a sensitivity of 79%. While conventional imaging modalities provided similar information in 80% of those patients, PET identified the primaries in an additional 14% (151).

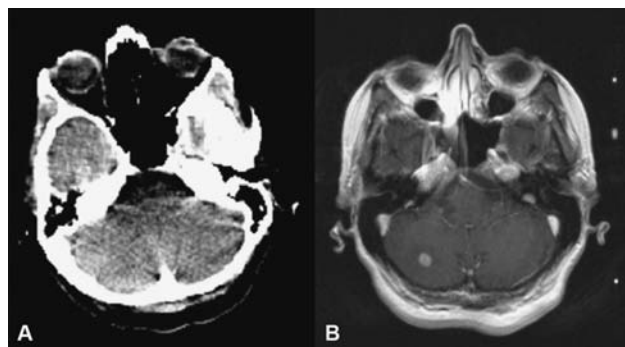


Figure 14 This woman with lung cancer underwent a PET/CT. The CT scan (A) performed in that study with a large field of view and low dose fails to demonstrate a lesion in the cerebellum. FDG PET (not shown) was also negative. Two weeks later a Gadolinium-enhanced MRI (B) shows a small lesion in the right cerebellar hemisphere. *Abbreviations:* PET, positron emission tomography; CT, computed tomography; FDG, ^{18}F -fluoro-2-deoxy-D-glucose; MRI, magnetic resonance imaging.

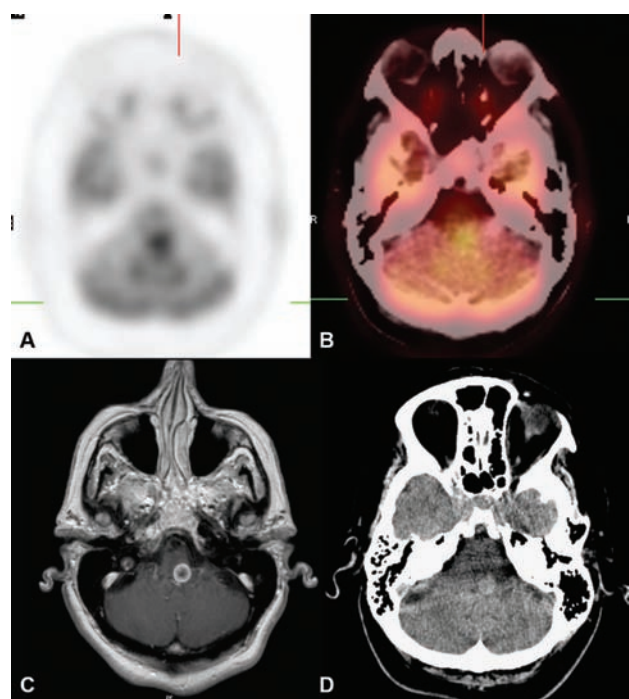


Figure 15 59-year-old woman with a history of ovarian carcinoma who presented with ataxia. Transaxial PET study (A) and fused PET/CT (B) show a focus of increased uptake in the posterolateral left medulla. The postcontrast T1-weighted axial MRI (C) shows ring enhancement and the lesion appears slightly hyperdense on noncontrast CT obtained with the PET (D). *Abbreviations:* PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

Follow-up of Brain Tumors

The follow up of patients with low-grade gliomas focuses on early identification of progression or recurrence which occurs at a median of around seven to eight years from diagnosis (152). While MRI is the standard, FDG PET may show malignant degeneration well before MRI or CT and for that reason will provide better prognostic information (153–155) (Fig. 16). In the follow up of irradiated brain tumors, the differentiation of radiation necrosis from tumor recurrence is a key problem in patients who present with neurologic deterioration. Radiation necrosis can mimic tumoral disease on conventional cross-sectional imaging with nodular areas of enhancement, mass effect, and edema. FDG PET has been found to have prognostic value in such patients (155,156) with those who demonstrate increased FDG uptake on PET having a shorter overall survival. Much was initially made of the utility of FDG because of its high sensitivity (80–90%) (157); however, it has become clear from animal models that FDG uptake by macrophages in radiation necrosis can cause false positives (158). This uptake is more likely to occur within the first three to four months following radiation (157). Indeed, after irradiation in a group largely treated with radiosurgery, FDG PET was found to have a high positive predictive value (>90%) but a fairly low negative predictive value (156) (Fig. 17). The specificity in another series of 84 patients with previously treated glioma was only 22% when compared with white matter uptake, but 56% when compared with gray matter uptake (159). The false positives occurred in radiation-induced necrosis. In metastatic lesions treated with radiosurgery, FDG PET performed an average of 33 weeks after treatment added specificity to MRI in identifying residual tumor. Sensitivity of PET (75%) was lower than that of MRI (91%), but the specificity (94%) exceeded the specificity of MRI (65%) (160) (Fig. 18).

Advanced MRI Techniques

Today, imaging of brain tumors is dominated by MRI. Therefore, a brief description of the role of advanced MRI techniques is warranted. Of interest, MRI techniques including perfusion and spectroscopy offer some of the same potential benefits as functional PET imaging including improved estimation of extent of tumoral disease, differentiation of tumor types (including primary versus metastatic neoplasm), follow-up after treatment (161–164) as well as functional/metabolic information which complements the anatomic information obtained by conventional MRI. Much research is currently underway in the use of perfusion and spectroscopy in brain tumor diagnosis and treatment.

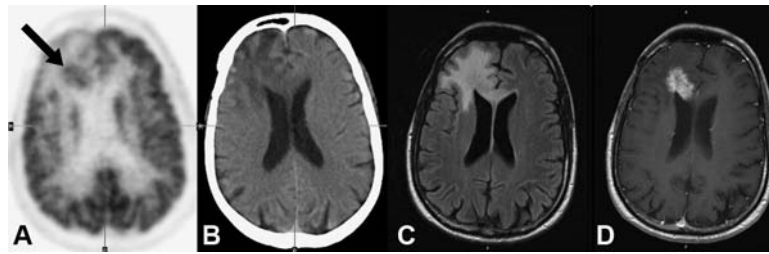


Figure 16 49-year-old man with recurrent glioblastoma multiforme. Transaxial FDG PET (A) demonstrates increased uptake (arrow) corresponding to low attenuation seen in the right frontal white matter on the CT (B). The FLAIR MRI image (C) shows increased signal in the right frontal white matter and a vague area of relatively lower signal adjacent to the frontal horn of the right lateral ventricle which corresponds to an underlying mass lesion, better demonstrated on postcontrast T1 (D) MRI. *Abbreviations:* FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

The most common MRI perfusion technique is a first pass, T2-weighted dynamic susceptibility gadolinium-enhanced technique. Perfusion imaging exploits the presence of abnormal vessels and of neovascularity/angiogenesis associated with tumors. Perfusion imaging allows for quantification of cerebral blood volume, cerebral blood flow, and permeability. Cerebral blood volume has been shown to correlate well with tumor type (differentiating primary from metastatic lesions) and tumor grade (with high grade gliomas showing greater perfusion). MRI perfusion can also help to direct stereotactic biopsy (162,165).

Proton MRS is a powerful method that allows for the in vivo interrogation of brain and tumoral metabolites. Both single voxel and multivoxel evaluation is possible. Single-voxel interrogation is useful for quantitative analysis and typically a large voxel (on the order of 1–2 cm in one dimension) is used to improve signal to noise; this technique is best suited for larger tumors with solid components that fit completely within the voxel so as to decrease contamination. Multivoxel analysis generally utilizes smaller voxels with lower signal to noise, but allows for comparisons between multiple areas.

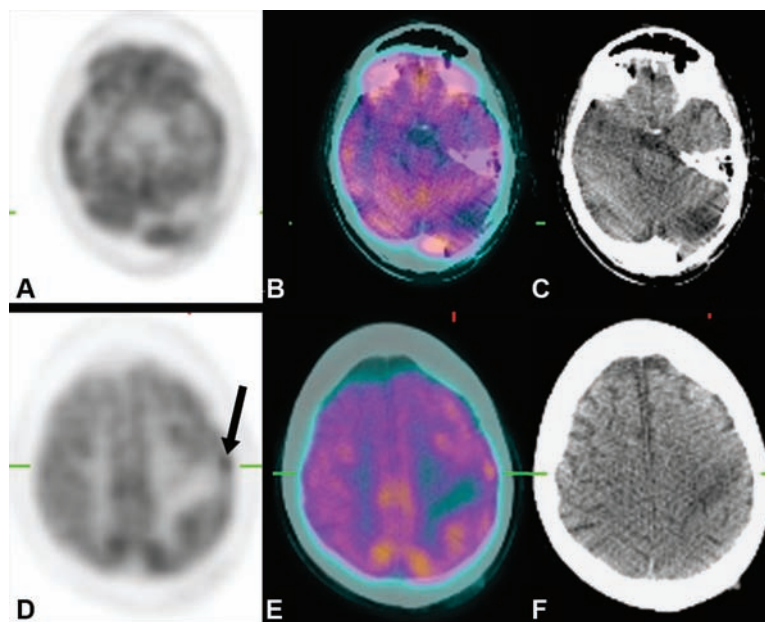


Figure 17 73-year-old man found to have non-small cell lung cancer. He presented with a left cerebellar lesion which was resected and found to be an adenocarcinoma. Subsequently, a second lesion in the left frontoparietal brain was treated with radiosurgery. One week later he underwent an FDG PET/CT. The site of surgical resection in the left cerebellum shows the expected absence of metabolic activity on PET (A) fusing (B) to the surgical defect on CT (C). The PET shows (D) a focus of increased uptake (arrow) at the radiosurgery site fusing (E) to the cortex near the decreased density seen on CT (F). *Abbreviations:* FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography; CT, computed tomography.

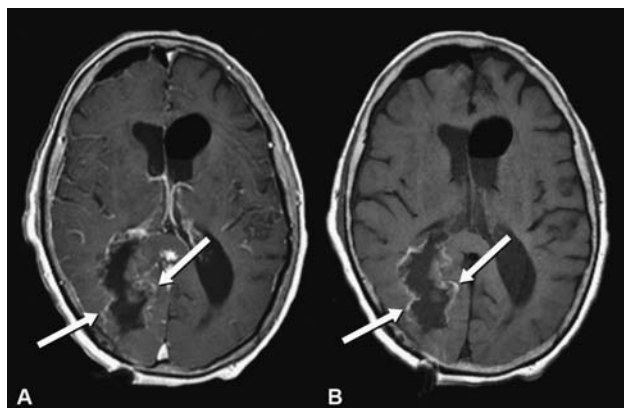


Figure 18 An 89-year-old woman presented with a brain mass found at resection to be an anaplastic mixed tumor with some cells of oligodendrocytic lineage and some of astrocytic lineage. Post-resection, apparent hyperdensity adjacent to the surgical cavity (arrows) on the postcontrast MRI (A) is not enhancement as it is present on the precontrast images (B) and represents hemorrhage. The bright signal at the surgical site on both images represents blood. *Abbreviation:* MRI, magnetic resonance imaging.

Both MRI perfusion and MR techniques can show abnormalities in areas outside of the enhancing abnormality (162,166). Recent work in diffusion tensor imaging shows that this technique is able to demonstrate white matter involvement to a high degree (167,168).

MRS has also shown promise in differentiating between radiation necrosis and recurrent tumoral disease (169,170). One group found they were able to correctly classify 27 of 28 cases using a 1.8 cutoff value for Cho/Cr (choline/creatine) and NAA/Cho ratios (171). The choline peak represents several choline-containing metabolites, some of which are precursors to phosphatidylcholine, present in cell membranes. In MRS, choline is believed to be frequently elevated in tumoral tissues because of high cellular turnover (172). Other groups have reported lack of hyperperfusion on MRI perfusion imaging in radiation necrosis compared with recurrent tumor (173,174). As all of these techniques evolve, it may be that metabolic imaging using radiotracers and advanced MRI techniques will be complementary and, used together, the hope is to improve imaging and understanding of CNS neoplasms so that treatment approaches will become more effective.

EPILEPSY IMAGING

The clinical approach to patients with refractory epilepsy involves a broad range of evaluations including neurologic examination, psychiatric evaluations, neuropsychologic testing, video-surface electroencephalogram (EEG) monitoring both during the interictal and the ictal states, WADA tests, invasive or subdural EEG, and MEG. As

with many of these examinations, the role of imaging in epilepsy is twofold: to detect structural abnormalities which may cause seizures and to aid in presurgical planning (175) since surgery will render 55–70% of patients with temporal lobe epilepsy and up to half of patients with extratemporal lobe epilepsy seizure-free (176). Functional neuroimaging, either metabolic interictal FDG PET imaging or ictal, interictal or subtraction cerebral perfusion SPECT, is most often performed to help localize a seizure focus for presurgical planning. In addition, there is evidence that postsurgical neurofunctional imaging may help predict outcome. In addition, deficits on FDG PET may reflect secondary effects of seizure activity, either in terms of temporary deafferentation or more permanent, long term damage caused by seizure activity.

The role of CT by itself is limited in the evaluation of epilepsy. CT is used mainly to assess for acute CNS abnormalities resulting in seizure, e.g., acute intracranial hemorrhage, which will appear hyperintense to normal brain tissue on unenhanced CT examinations. Frequently, calcifications are best appreciated on noncontrast CT using bone windows, although susceptibility artifact from calcification can also be seen on MRI. Punctate foci of calcifications within the brain parenchyma are usually postinflammatory/ postinfectious and they can result in seizures, particularly if they are cortically based.

In the setting of epilepsy, MRI is the preferred anatomic cross-sectional modality. As with CT, the first role of cross-sectional imaging in MRI is to exclude gross anatomic abnormalities, which may result in seizures including mass lesions, congenital abnormalities of neuronal migration, e.g., schizencephaly and cortical dysplasia, and areas of traumatic brain injury. In the evaluation of patients with partial complex seizures and temporal lobe epilepsy, recent research efforts in the imaging of mesial temporal sclerosis focus on three main areas: improving localization of epileptogenic foci, predicting postsurgical outcome, and elucidating the natural history of the disorder (177,178). Various advanced MRI techniques have been reported in the evaluation of mesial temporal sclerosis including diffusion-weighted imaging (179), diffusion tensor imaging, T2 relaxometry (180,181), MRS (40,182), and functional MRI. Investigators have also begun using high field MRI to evaluate these patients with promising initial reported results (183).

For localization of seizure foci for presurgical planning in patients with refractory epilepsy, the most successful outcomes occur when there is agreement among multiple types of examinations and monitoring (184). Surgical treatment is usually reserved for mesial temporal lobe epilepsy or in the neocortex, perilesional epilepsy (185). The most common pathologic finding in adult patients with temporal lobe epilepsy is mesial temporal sclerosis

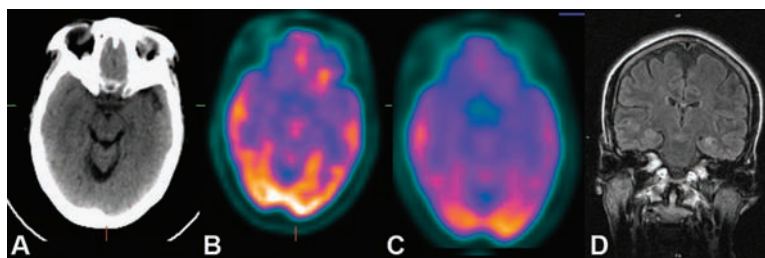


Figure 19 34-year-old woman with medically intractable epilepsy. CT scan (A) from the PET/CT spuriously suggests volume loss in the left temporal lobe because of the tilt of the patient's head. The corresponding PET slice (B) also suggests decreased metabolic activity in the left temporal lobe. However when this interictal PET was reoriented (C) to level the brain in the coronal plane, there is still an asymmetry suggesting a left temporal seizure focus. Coronal MRI (D) shows left mesial temporal sclerosis. The patient went on to a left temporal resection with a seizure free outcome. *Abbreviations:* CT, computed tomography; PET, positron emission tomography.

(186). Thin section coronal T1 weighted, T2-weighted, and FLAIR images are typically performed through the temporal lobes as part of the routine MRI evaluation of epileptic patients to evaluate for volume and signal abnormalities of the mesial temporal structures (175). Hippocampal atrophy is usually seen as an asymmetric loss of hippocampal volume. This atrophy can be appreciated both quantitatively and qualitatively. Bilateral hippocampal atrophy can be hard to perceive qualitatively. Much work has been done in the area of hippocampal volumetric analysis with excellent correlation between seizure focus laterality and the side of MRI abnormality (187). Mesial temporal sclerosis technically is a pathologic term that describes a loss of pyramidal neurons and gliosis (186,188). On MRI, sclerosis is suspected when T2 prolongation is identified in the mesial temporal structures. Frequently, this is best appreciated on coronal FLAIR images as there is suppression using inversion recovery techniques of the CSF (Fig. 19). In severe cases, ipsilateral limbic system structures may also be involved and appear atrophic including the mamillary body and fornix. However, MRI may be normal in 29% to 50% of patients with temporal lobe epilepsy (185,189).

FDG PET has a very high sensitivity for localizing seizure foci in mesial temporal lobe epilepsy (80–90%) (190). PET has been found to be localizing in 44% of patients with temporal lobe epilepsy even when MRI is normal (185) and will help lateralize the seizure focus in 57% of patients, who following surgical resection on the basis of these findings, became seizure free. Others have confirmed that regardless of the presence or absence of mesial temporal sclerosis on MRI, lateralization by PET predicts a good outcome (191), although it may imply a neocortical lateral temporal lobe focus. Others have suggested that mesial and anterior temporal lobe hypometabolism alone is more likely to occur in the presence of hippocampal sclerosis, but in the presence of other lesions, lateral or neocortical temporal lobe will more

likely be involved (192). Furthermore, in this subset of patients, FDG PET and cerebral perfusion SPECT may be complementary since one may be localizing when the other is not. In pediatric temporal lobe epilepsy ictal SPECT and visual assessment of PET have comparable sensitivity (193). Statistical parametric mapping analysis sometimes has been more sensitive than qualitative visual assessment in detecting areas of hypometabolism in some investigators' hands (193–195) and more sensitive in identified asymmetry when there is visually bilateral hypometabolism (195).

The greater the asymmetry and the more profound the hypometabolism in the temporal lobe on PET, the better the postoperative outcome is for patients (189,196,197). The presence of localized hypometabolism on FDG PET in general is more likely to be associated with a seizure-free surgical outcome in patients with neocortical epilepsy along with a localized lesion on MRI or localizing ictal EEG (195). When bilateral mesial temporal hypometabolism is present, EEGs are more likely to show bilateral abnormalities and surgical outcomes, both in terms of memory loss and recurrent seizures, are likely to be less favorable (194).

Sensitivity appears to increase as the duration of the seizure disorder increases. One study found a 20% incidence of focal hypometabolism in children with seizure disorders of less than a year's duration (198), which is lower than in the adult population. In children with a more prolonged history of seizures, FDG PET contributes to localization of the epileptogenic focus in 50% (199), leads to a change in surgical management in over half, and offers useful information in about three fourths of pediatric patients. The underlying pathophysiology of hypometabolism may be either neuronal loss secondary to the effects of epilepsy, or functional depression of metabolism secondary to deafferentation (200). In children the onset of developmental delay after the onset of seizures may reflect the neuronal insult caused by seizure activity (201).

The latter is supported by the reversal of relatively distant or contralateral areas of hypometabolism after successful surgical treatment of epilepsy. Also, ipsilateral thalamic, basal ganglia, and adjacent frontal lobe hypometabolism in patients with neocortical temporal lobe epilepsy has been observed, which may support the notion of diaschisis (191,202), but others have described increasing incidence and severity of thalamic hypometabolism with longer durations of epilepsy, both temporal and frontal lobe suggesting that neuronal damage may also underly the hypometabolism (203). In other epileptic syndromes, seizure activity in the mesial temporal lobes has been associated with frontal lobe hypometabolism (204).

Occipital lobe epilepsy is much less common than temporal lobe epilepsy and is clinically characterized by auras with visual hallucination or illusion, blindness or field deficits (205). FDG PET has shown about 67% sensitivity for lateralizing a seizure focus in patients with occipital lobe epilepsy with less specificity than MRI (205). In generalized infantile tonic-clonic seizures, PET abnormality is frequently multifocal or generalized. In these patients, hypometabolism in the frontal lobes correlates with neuropsychologic changes and developmental abnormalities as well as ataxia and hypotonia (206). Temporomesial deficits in this setting are seen in children who become obtunded during seizures and central and parietal deficits tend to be seen in those with myotonic manifestations. In patients with epilepsies having continuous spikes and waves during sleep, FDG PET is frequently abnormal though hypometabolic areas are not localizing (204) and while some investigators have seen a preponderance of temporal lobe hypometabolism, other reports disagree. Areas of hypermetabolism, on the other hand, are likely related to ongoing interictal spikes on EEG and this has been previously described (204).

Focal mass lesions, particularly cortical lesions, can also result in focal epilepsy. In general, these are well evaluated by MRI and include lesions such as vascular malformations, primary and secondary neoplasms, both benign and malignant, as well as regions of cortical dysplasia and areas of parenchymal hemorrhage due to prior traumatic brain injury.

Patients with phakomatoses such as tuberous sclerosis and, less frequently, neurofibromatosis I (207) can have intractable seizures because of cortical abnormalities. Seventy to ninety percent of patients with tuberous sclerosis will have epilepsy (208). Tuberous sclerosis complex is an autosomal dominant disorder that most commonly occurs as a spontaneous mutation, that is characterized by the clinical triad of cutaneous lesions, mental deficiency, and seizures. The disease may result in significant morbidity and may be the underlying cause of infantile spasms (209). MRI provides a sensitive indication of the number, size, and location of cortical tubers (210), which are the

most characteristic CNS lesions of the disease, seen in approximately 95% of patients (211). Cortical tubers are seen as cortical, and sometimes subcortical, areas of signal abnormality on T2 and FLAIR images. Twenty percent of lesions have associated mass effect. Enhancement within the lesions is not typical but can be seen. Additional CNS findings include white matter hamartomas and subependymal nodules that can calcify. There is also an association between tuberous sclerosis and subependymal giant cell astrocytomas that usually occur at the foramen of Monro (211,212).

While MRI is useful in making the initial diagnosis and thereby identifying patients who may benefit from surgical treatment (213), localization of the epileptogenic tuber remains a challenge as patients usually have multiple lesions, any one or more of which may be the source of the epileptogenic focus. FDG PET will show hypometabolism associated with tubers. In patients with subependymal nodules, periventricular and deep white matter hypometabolism has also been described (214,215) but commonly, the metabolism in tubers is similar to that of normal gray matter and is not localizing interictally with FDG PET. Furthermore, with children less than one year of age, the normal regional brain hypometabolism may mask the tuber-associated abnormalities (216). C-11 α -methyl-L-tryptophan (AMT) has been found useful to identify the epileptogenic tubers (217,218) and appears to be associated with the site of interictal spikes on EEG (219). The specificity of AMT is greater than FDG PET for localization of epileptogenic tubers (220). C-11-flumazenil, also not currently widely available, appears to be comparable with FDG in localization of the epileptogenic focus but may depict a smaller area of abnormality, presumably representing the actual seizure focus (221).

Cortical dysplasia has been implicated in up to 20% of intractable epilepsy treated with surgery (222) and is the most common MRI (223) abnormality associated with infantile spasms. Cortical dysplasia may be a more common underlying pathology in patients with frontal lobe epilepsy than in those with temporal lobe foci (224). Focal cortical dysplasia is part of a spectrum of diseases of cortical development, which also includes lissencephaly and heterotopia (Fig. 20). The most common presentation is medically refractory epilepsy. Focal cortical dysplasia is an abnormality of neuronal migration, although the factors resulting in abnormal migration are believed to be both genetic and congenital. Pathologic findings divide focal cortical dysplasia into two groups: those containing abnormal neurons and balloon cells (Taylor type) and those demonstrating architectural distortion without abnormal cells (225). MRI findings of cortical dysplasia include cortical thickening, thinning or paucity of the underlying white matter (Fig. 20), and, in a quarter of patients, signal abnormality on T2 weighted and FLAIR sequences (211).

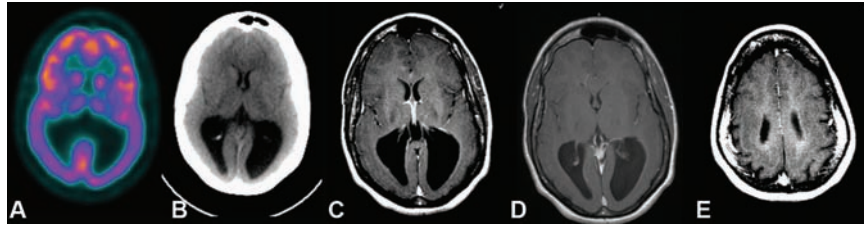


Figure 20 39-year-old woman with refractory epilepsy and neuronal migration anomaly. FDG PET (A) and corresponding CT (B) slice show the loss of white matter in the posterior brain with colpocephaly and pachygyria. MRI T1-weighted (C) and FLAIR images (D) again show the relative paucity of white matter posteriorly in this neuronal migration abnormality. T1-weighted images at a more cephalad level show band heterotopia (E). Neither PET nor MRI was helpful in localizing the seizure focus in this patient with extensive abnormality. *Abbreviations:* FDG, ^{18}F -fluoro-2-deoxy-D-glucose; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

Focal cortical dysplasia can, however, be extremely subtle on even high resolution MRI and sometimes no abnormality is detected. MRI is used in conjunction with intra-operative EEG to localize lesions and to best attempt a complete resection of the abnormality (225).

While FDG is a more sensitive indicator of focal cortical dysplasia (226), the extent of MRI abnormality tends to correlate better with pathologic type (227). In Taylor type focal cortical dysplasia, FDG PET uptake tends to localize within areas having higher prevalence of abnormal cells including balloon cells and cytomegalic neurons (228). Because surgical treatment should aim at resection of the entire dysplastic region (229), and because other dysplastic areas may become epileptogenic after limited resections (230), FDG has limited use in directing successful surgical intervention. The extent of FDG delineated hypometabolism tends to overestimate the size of the epileptogenic focus relative to MRI abnormalities (227) and may even extend beyond the confines of the cortical dysplasia. Of note, hypometabolism in a suspected epileptogenic region of cortical dysplasia is associated with better surgical outcomes (224).

Studies using benzodiazepine receptor ligands such as C-11-flumazenil have shown more specific localization within cortical dysplasias (231) and may also show abnormalities in the absence of MRI findings (232). Interestingly, C-11 MET will show focally increased uptake in these dysplastic lesions (233). Similarly, another C-11 labeled agent, AMT, a serotonin receptor ligand, can localize seizure foci in cortical dysplasia in the absence of F-18 FDG PET abnormalities (219).

The use of FDG PET after surgery has been used to show the effects on the brain of removal of the seizure foci. After resection of epileptogenic mesial temporal lobes, PET will often show an increase in the ipsilateral anterior insular cortex and frontal lobe as well as the anterior thalamus relative to presurgical metabolism (234–236). These changes are felt to reflect the recovery of brain previously inhibited by interictal and ictal discharges. Other areas may

show a decrease in metabolism after surgery to areas of the thalamus and ipsilateral striatum, probably because of deafferentation from the resected brain (234).

CONCLUSION

In summary, FDG PET/CT will continue to play a major role in diagnosing the underlying type of dementia in the elderly. The pattern of uptake on FDG PET with evidence of progression on serial studies will enhance confidence in the diagnosis. While FDG PET can differentiate AD from frontotemporal lobar degeneration, the subtypes of FTD are less easily distinguished with qualitative, visual inspection. Statistical parametric mapping may prove helpful in this regard.

MRI remains the mainstay of imaging evaluation for brain tumors whether primary, metastatic, or treated. There may be a continued role for FDG PET in evaluating recurrent tumors when MRI is equivocal and in biopsy, surgery, and radiation planning. Other agents based on amino acids, when they become available clinically, may prove more definitive.

In epilepsy, interictal FDG PET can be helpful in localizing seizure foci with fairly high sensitivity and specificity when MRI and CT are unremarkable. Once MRI or CT show focal or generalized abnormalities, interictal PET is likely to be less useful. Other applications of FDG PET such as in evaluating the sequelae of traumatic brain injury, in psychiatric disorders, or in chronic inflammatory disease show less clear-cut utility in the clinical setting.

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5

Head and Neck Cancers: Evaluation with PET/CT

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INTRODUCTION

A successful clinical outcome for patients with head and neck cancers depends heavily on accurate staging and tailoring of the treatment on the basis of that staging. While clinicians have relied on computed tomography (CT) and magnetic resonance imaging (MRI) for this in the past, fluorodeoxyglucose positron emission tomography (FDG PET) alone has offered some promise, particularly in the identification of locoregional lymph node involvement, distant metastases, and second primary tumors. PET also has taken an acknowledged role in identifying the primary tumors in patients with carcinoma of unknown primary malignancies, as well as in staging them. With the advent of in-line PET/CT the utility of these modalities has become unequivocal. Imagers are no longer burdened by the difficulties in distinguishing normal from abnormal metabolic activity and can take advantage of the increase in sensitivity that adding PET to CT affords.

CT Acquisition Techniques

Although there is no single way to acquire a CT of the head and neck, and CT technique will be strongly influenced by the accompanying PET scan with an in-line PET/CT,

adherence to certain guidelines will facilitate identification of anatomy both for diagnosis and for tumor staging.

The head and neck should be scanned in neutral position, that is when the hard palate is perpendicular to the scanning table, and with arms and shoulders down (1). The smaller, preferred field of view (16–18 cm) will not be used in the PET/CT although post scan reconstructions with smaller fields of view may improve on image quality. Intravenous contrast should be used whenever possible and thinner slices for diagnostic CT, usually 2 to 3 mm, are recommended (1).

PET Protocol Considerations

The technique employed in acquiring PET/CT of the head and neck region is designed to optimize visualization of uptake patterns while minimizing artifacts that degrade image quality, and thus, interpretation. A minimum of four hours fasting time is required, during which only water is permissible. Generally, oral contrast is not administered for this study in order to prevent increased muscle uptake in the neck and oropharynx and may obscure small foci of increased radiopharmaceutical accumulation suspicious for malignancy (Fig. 1). It is especially important to limit talking during the uptake phase in

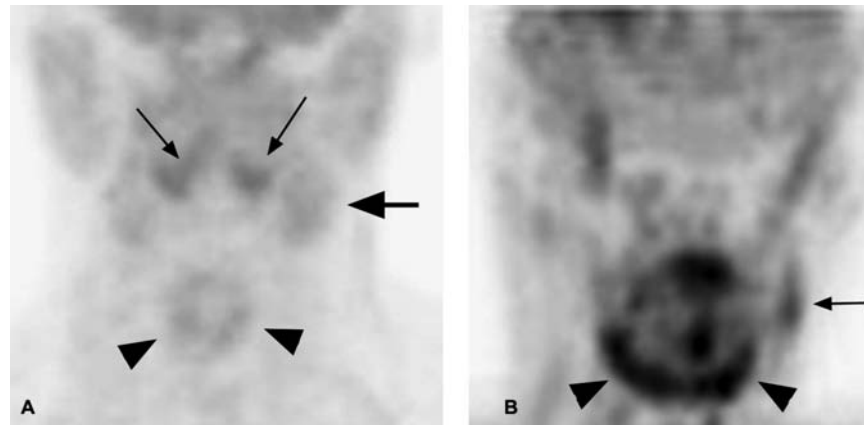


Figure 1 Physiologic distribution of FDG. (A) Coronal FDG PET image demonstrating physiologic distribution of radiopharmaceutical in the tonsils (*small arrows*), salivary glands (*large arrow*), and larynx (*arrowheads*). (B) Coronal FDG PET image which illustrates increased oral cavity uptake (*arrowheads*) as well as head and neck musculature (*arrow*) activity due to excessive swallowing during the uptake phase.

the head and neck patients, again to minimize physiologic uptake in muscles. In the previously treated patient, muscle uptake may be asymmetrical.

PET/CT Protocol Considerations

Intravenous contrast material, if administered, should have an adequate delay between injection time and CT scan acquisition, 80 to 90 seconds, so as to effectively eliminate the possibility of artifacts in the neck region. However, recently PET/CT with intravenous contrast has been performed with a 30-second delay between the beginning of the contrast injection and scan acquisition using 70 cc of contrast (2). In order to reduce beam-hardening artifacts created by raised arms in the CT in the attenuation-corrected PET images, patients should be positioned and scanned with their arms down. If this subsequently causes distortion in the region of the chest, two acquisitions may be performed: one with the arms down from the vertex of the skull to the midsternum; the second with the arms raised, from the base of the skull to the mid-femurs. It is necessary to obtain images through the body, at minimum including the liver, in order to more accurately stage the patient, as well as evaluate for synchronous or metachronous second primary malignancies, which occur in approximately 26% to 56% of patients with carcinomas of the head and neck (3–5). In patients with an unknown primary malignancy, it is advantageous to acquire images through the pelvis.

CT ANATOMY

Head and neck anatomy is complex and challenging. Although it is beyond the scope of this chapter to provide a detailed anatomical foundation, key imaging anatomy

(Table 1) will be reviewed in order to facilitate in imaging interpretation. The pharynx is a musculomembranous tube that extends from the skull base to the esophageal verge. The pharynx is divided into three separate components: the nasopharynx, oropharynx, and hypopharynx.

Nasopharynx

The nasopharynx extends from the nasal choanae underneath the skull base to the soft palate (Fig. 2). The lateral walls are formed by the margins of the superior constrictor muscles.

Anteriorly, the nasopharynx communicates with the nasal cavity by the posterior nasal choanae. Below the nasopharynx lies the oral cavity anteriorly and the oropharynx posteriorly. The mucosa of the nasopharynx is separated from the deep retropharyngeal space by the pharyngobasilar fascia, which forms a rather stiff barrier to the spread of mucosal diseases. The posterior portion of the nasopharynx has a characteristic appearance on cross-sectional imaging studies with three important structures that are easily identified (Fig. 3): the Eustachian tube orifice, the torus tubarius, and the lateral pharyngeal recess or fossa of Rosenmüller. The Eustachian tube orifice is the most anterior structure, which allows for the direct communication of the middle ear with the nasopharynx. On either side of the Eustachian tube orifice lie the tensor (anterolateral) and levator (posteromedial) veli palatine muscles. These muscles elevate and tense the soft palate. Posterolateral to these muscles lies the parapharyngeal space that is predominately filled with fat. Just posterior to the Eustachian tube orifice is a cartilaginous structure, the torus tubarius. Finally, just behind, and superior to the torus tubarius is a mucosal reflection that overlies the lateral aspect of the longus coli and longus

Table 1 Important Head and Neck Anatomy on CT

Nasopharynx	- Eustachian tube opening - Torus tubarius - Fossa of Rosenmüller (lateral pharyngeal recess)
Oropharynx	- Soft palate - Uvula - Posterior one-third of the tongue (tongue base) - Palatine tonsils - Anterior tonsillar pillar - Posterior tonsillar pillar - Lingual tonsils - Valleculae - Pharyngeal constrictors (posterior and lateral walls)
Oral cavity	- Lips - Hard palate - Upper and lower alveolar ridges - Anterior two-third of the tongue - Buccal mucosa - Retromolar triangles - Floor of the mouth
Hypopharynx	- Posterior hypopharyngeal wall - Pyriform sinuses - Post cricoid region
Supraglottic larynx	- Epiglottis - Preepiglottic space - Aryepiglottic folds - False cords - Paraglottic space - Laryngeal vestibule - Laryngeal ventricle
Glottic larynx	- True vocal cords - Anterior commissure - Posterior commissure

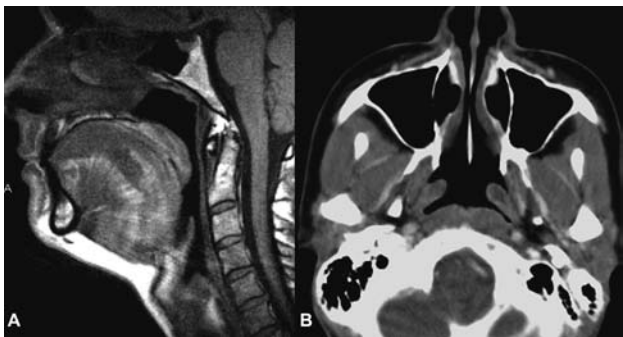


Figure 2 Boundaries of the nasopharynx. (A) Sagittal reformat of a CT. (B) Axial CT at the level of the nasopharynx and the choanae. The nasopharynx extends from the skull base to the soft palate. Anteriorly, the nasopharynx is bound by the choanae that connect the nasal cavities to the nasopharynx. The parapharyngeal spaces are at the lateral boundary.



Figure 3 Anatomy of the nasopharynx. The posterior portion of the nasopharynx has a characteristic appearance on cross-sectional imaging; the Eustachian tube opening (*yellow arrow*), the fossa of Rosenmüller or the lateral pharyngeal recess (*red arrow*), and the torus tubarius (*white arrow*) are seen on this contrast enhanced CT.

capitus muscles, the fossa of Rosenmüller (6). Nasopharyngeal carcinoma (NPC) commonly originates around the fossa of Rosenmüller and spreads into the parapharyngeal and retropharyngeal spaces. Adenoidal lymphoid tissue is also commonly seen within the nasopharynx and, typically, should regress by the fourth decade of life. The adenoids, palatine tonsils, and lingual tonsils make up Waldeyer's ring of lymphoid tissue.

Oropharynx

The oropharynx is located between the soft palate and the tongue base (Fig. 4). The oropharynx contains the posterior one-third of the tongue (tongue base), the valleculae, and the palatine tonsils; the posterior and superior pharyngeal walls form the level of the soft palate inferiorly to the tip of the epiglottis, the uvula, and the body and undersurface of the soft palate (Fig. 4). The tongue base is the portion of the tongue located behind the circumvallate papillae and is filled with lymphoid tissue, which forms the lingual tonsil. The tongue base is bordered laterally by the glossotonsillar sulcus. The valleculae are paired air-filled depressions between the base of the tongue and the anterior surface of the epiglottis. The median glossopiglottic fold separates the right and left valleculae and

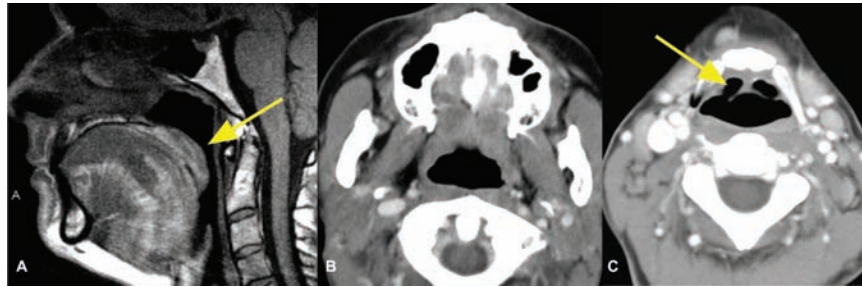


Figure 4 Boundaries of the oropharynx. Superiorly, the oropharynx includes the soft palate (*arrow*), which separates the nasopharynx from the oropharynx. (A) Sagittal reformat of a CT and (B) axial section at the level of the soft palate. (C) Inferiorly, the oropharynx extends to the level of the valleculae (*arrow*).

connects the tongue base to the anterior portion of the epiglottis. The palatine tonsils are paired structures which comprise the lateral borders of the oropharynx. The palatine tonsil, which is filled with lymphoid tissue, is situated within the tonsillar fossa which is bounded by the anterior and posterior tonsil pillars which are formed by the palatoglossus and palatopharyngeus muscles.

Oral Cavity

The oral cavity encompasses the area of the neck below the sinonasal cavity and anterior to the oropharynx. The oral cavity is separated from the oropharynx by the soft palate, anterior tonsillar pillars, and circumvallate papillae. The superior border is the hard palate and upper alveolar ridge, while the inferior boundary is the floor of the mouth, which is formed by the mylohyoid muscle and separates the submandibular and sublingual spaces. The lateral margins include the buccal mucosa. The anterior two-thirds of the tongue comprise the oral tongue. The musculature of the oral tongue is composed of intrinsic

and extrinsic muscles. The extrinsic muscles of the tongue are named for their attachments and insertions and consist of the genioglossus, hyoglossus, styloglossus, and palatoglossus muscles. The posterior one-third of the tongue, which is filled with lingual tonsillar tissue, however, is part of the oropharynx. The retromandibular molar triangle (RMT) is a triangular area of mucosa behind the last mandibular molar and immediately anterior to mandibular ramus. The significance of the RMT is that it serves as a conduit for squamous cell cancers to spread via the pterygomandibular raphe, a band of connective tissue, superiorly into the masticator space and inferiorly into the floor of the mouth.

Hypopharynx

The hypopharynx is part of the aerodigestive structure situated between the oropharynx and the larynx. The hypopharynx is divided into three distinct regions (Fig. 5): (1) the pyriform sinuses, (2) the postcricoid region, and (3) the posterior hypopharyngeal wall.

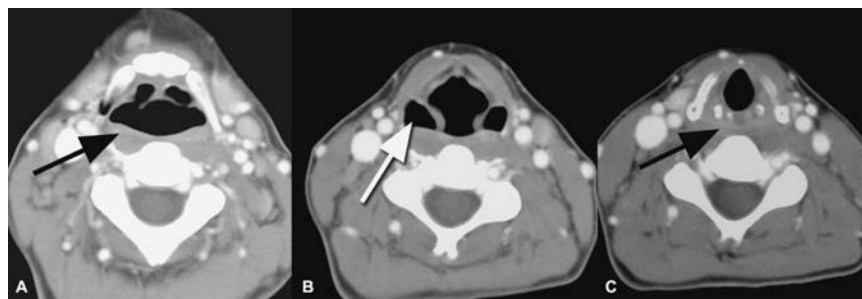


Figure 5 CT anatomy of the hypopharynx. The hypopharynx has three distinct regions: (A) Posterior hypopharyngeal wall (*arrow*), (B) pyriform sinuses (*arrow*), and (C) postcricoid region (*arrow*). The posterior hypopharyngeal wall is a continuation of the posterior wall of the oropharynx. Caudally, it merges with the posterior wall of the cricopharyngeus muscle and then the cervical esophagus. The pyriform sinus is an anterolateral recess of the hypopharynx situated on either side between the inner surface of the thyrohyoid membrane and thyroid cartilage laterally and the AE fold medially. The most caudal portion of the pyriform sinus (apex) lies at the level of the true vocal cord. Tumor confined to the medial aspect of the aryepiglottic fold will behave as a supraglottic tumor while a tumor confined to the lateral aspect of the aryepiglottic fold will behave as an aggressive hypopharyngeal tumor. The postcricoid region extends from the level of the arytenoid cartilage down to the lower edge of the cricoid cartilage.

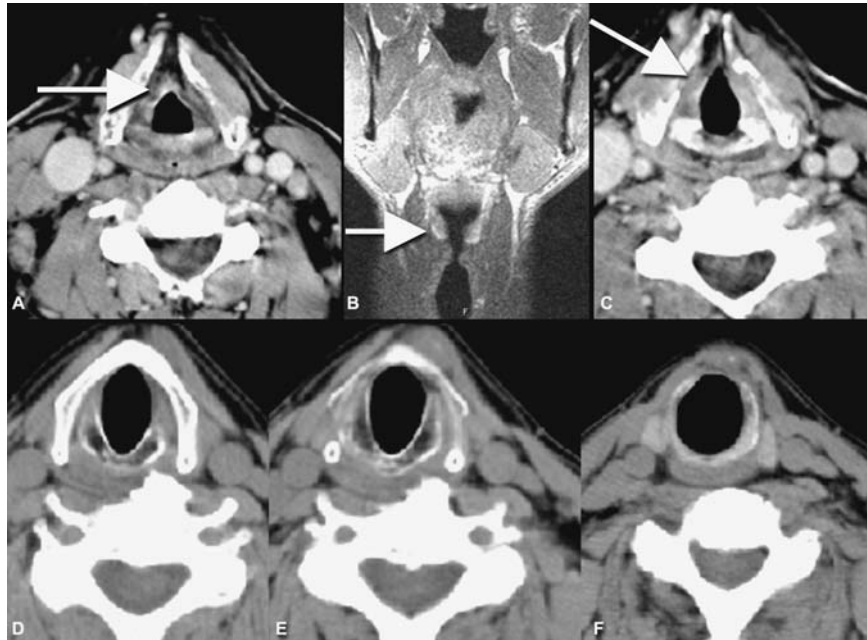


Figure 6 CT anatomy of the larynx. (A) False cords (*arrow*) in axial section and (B) coronal section are paired mucosal folds (*arrow*) running from the arytenoids to the inner thyroid lamina. They are predominantly fat. (C) True cords (*arrow*). (D–F) Subglottic region extends from the undersurface of the true cords to the inferior surface of the cricoid.

The pyriform sinus is a paired mucosal sac lying lateral to the aryepiglottic fold, which is bounded superiorly by the pharyngoepiglottic folds and inferiorly by the cricoid cartilage. The aryepiglottic fold is considered part of the larynx. The postcricoid region or the pharyngeal-esophageal junction extends from the level of the arytenoid cartilage to the inferior margin of the cricoid cartilage. The posterior hypopharyngeal wall extends from the level of the valleculae to the cricoarytenoid joint.

Larynx

The larynx consists of a mucosa-covered cartilaginous framework, consisting of the thyroid, cricoid, and arytenoid cartilages, which is suspended from above from the hyoid bone by the thyrohyoid membrane and attached below to the trachea (Fig. 6). The epiglottis, composed of elastic fibrocartilage, is a leaf-shaped structure which serves as a lid to the voice box. The thyroid cartilage is the largest of the laryngeal cartilages, and forms the anterior and lateral walls that protect the inner structures of the larynx. The cricoid cartilage is a signet-shaped ring and forms the only complete ring of the laryngeal cartilage. The lower border of the cricoid cartilage marks the junction between the trachea and the subglottic area of the larynx. The arytenoid cartilage is a paired, pyramidal-shaped cartilage that sits atop the posterior cricoid cartilage lamina. The opening to the larynx is continuous with the pharyngeal airway.

The larynx is divided into three anatomic regions: (1) the supraglottis, (2) the glottis, and (3) the subglottis. The supraglottis extends from the tip of the epiglottis to and including the laryngeal ventricle. The laryngeal ventricle is a slit-like lateral out pouching of the vestibule, which separates the false vocal cords (above) from the true vocal cords (below). The supraglottis includes the laryngeal vestibule and ventricle, epiglottis, preepiglottic space (Fig. 7), aryepiglottic folds, false vocal cords, and the paraglottic space. The laryngeal vestibule is the air space



Figure 7 Preepiglottic space. The anterior margin of the preepiglottic space is the thyroid cartilage and thyrohyoid membrane. Posteriorly, the space is bounded by the ventral aspect of the epiglottis. It extends superiorly to the hyoid and inferiorly to the thyroepiglottic ligament.

within the supraglottic larynx. The false vocal cords represent the fold of mucosa between the laryngeal vestibule and the laryngeal ventricle. The paraglottic spaces are paired fatty spaces beneath the false and true vocal cords. The preepiglottic space is a C-shaped fat-filled space behind the hypoid bone and anterior to the epiglottis.

The glottis includes the true vocal cords and the anterior and posterior commissures (Fig. 6). The glottis extends from the lateral most apex of the laryngeal ventricle to an arbitrary line drawn 1 cm inferior to the inferior edge of the laryngeal ventricle. The anterior commissure is the midline anterior meeting point of the true vocal cords and should be less than 1 mm on cross-sectional imaging. The posterior commissure is the mucosal surface on the anterior margin of the cricoid cartilage between the arytenoids cartilages. The subglottis (Fig. 6) extends from the undersurface of the true vocal cords to the inferior edge of the cricoid cartilage.

Lymphatic drainage of the larynx has an embryologic basis. The supraglottic larynx is derived from the pharynx and has a rich lymphatic drainage, which can lead to high nodal recurrence rates (7). The glottis and subglottis are derived from the trachea and have sparse lymphatics. Glottic and subglottic squamous cell cancers have a low incidence of nodal metastases (8).

Lymph Nodes

Cervical lymph nodes were historically classified into specific groups on the basis of palpation and surgery. The American Joint Committee on Cancer (AJCC) guidelines for nodal staging subdivides the lymph nodes of the neck into specific levels. A system of levels is used to clinically describe the lymph node location. This level-concept takes into consideration tumor spreads to specific nodal levels rather than nodal chains. Som et al. (1) proposed a new imaging-passed classification that can easily be applied to axial cross-sectional anatomy.

When evaluating and identifying the location of lymph nodes, each side is considered separately. Table 2 (Figs. 8 and 9) provides a description of each nodal level. Tumors at each anatomic level of the neck tend to involve certain lymph node levels more often than others. For example, laryngeal tumors rarely involve level IA, but are likely to involve any other lymph node level of the neck (9,10). Supraglottic tumors tend to metastasize to level II and III nodes, but very rarely to level IB (11). Levels IV and V and supraclavicular lymph nodes are most often affected by subglottic and glottic tumors. Finally, high esophageal cancers tend to metastasize to level VI and VII nodes (superior mediastinal and paratracheal lymph nodes) (1). This concept becomes particularly important in the setting

of unknown primary cancers when patients present with a metastatic lymph node.

NORMAL PET FINDINGS

Interpretation of PET images in the region of the head and neck is complicated by physiologic variations of FDG distribution in anatomic structures, which cannot necessarily remain quiescent during the uptake phase. Musculature, lymphoid tissue and salivary glands have constant metabolic demands, and may demonstrate increased radiopharmaceutical accumulation although their activity is, in fact, physiologic. In interpreting the head and neck portion of the PET study, it is particularly important to correctly identify physiologic uptake versus possible malignancy. Although anatomical information provided from the concomitant CT scan may be useful, even very small degrees of misregistration may hinder clear interpretation. In such instances, knowledge of the general pattern of background activity in the head and neck is paramount.

Normal or increased FDG uptake may be identified in lymphoid tissue, salivary glands and musculature (Fig. 1). Lymphoid tissues, often more prominent in younger patients, such as the lingual, pharyngeal (adenoids), and palatine tonsillar tissues (Waldeyer's ring) demonstrate a range of metabolic activity, although in the native nasopharynx and oropharynx the expected pattern is symmetrical. More intense symmetrical uptake in this region is primarily attributed to infection or inflammation. Asymmetrical uptake in the tonsil or tonsillar fossa is more suggestive of malignancy in the proper setting (12).

Salivary glands may not be visualized or may demonstrate minimal diffuse activity. Focally increased FDG accumulation can indicate inflammation or infection such as sialoadenitis. Again, a factor favoring physiologic activity over malignancy or inflammation is symmetry.

The muscles of mastication, the masseter and the lateral pterygoid, may have symmetrically increased uptake, which given the bilateral nature of the activity usually indicates a physiologic process. Decreasing the voluntary use of these muscles, by advising patients to avoid excessive chewing (i.e., gum), will in turn decrease the level of FDG uptake. In addition, the base of the tongue, the floor of the mouth, and the laryngeal musculature including the mylohyoid and vocalis muscles also demonstrate increased baseline activity. In the neck, the sternocleidomastoid muscles as well as the scalene muscles can accumulate elevated amounts of radiopharmaceutical. More rarely the temporalis appear FDG-avid. Of note, occasionally the muscle insertions themselves may mimic metabolically active lymph nodes especially if only one orthogonal plane is reviewed.

Table 2 Imaged-based Classification of Lymph Node Levels

Level	Image-based classification	Anatomic location
I	• Anterior to the posterior aspect of submandibular gland • Superior to hyoid bone	Submental and submandibular
IA	• Inferior to mylohyoid muscle • Superior to hyoid bone • Inferior to mylohyoid muscle	Submental
IB	• Medial to anterior belly of each digastric muscle • Lateral to level 1A nodes	Submandibular
II	• Anterior to the posterior aspect of the submandibular gland • Between skull base and inferior margin of the hyoid bone • Behind the submandibular gland	
IIA	• Anterior to the posterior margin of the SCM muscle • Anterior, medial, or lateral to the internal jugular vein • If posterior, no intervening tissue or fat between the node and the internal jugular vein	Upper internal jugular nodes
IIB	• Posterior to the internal jugular vein with intervening fat	Upper spinal accessory nodes
III	• Inferior to the hyoid bone • Superior to the inferior extent of the cricoid arch • Anterior to the posterior margin of the SCM	Mid jugular nodes
IV	• Inferior to the bottom of the cricoid arch • Superior to the clavicle • Lateral to carotid arteries • Anterior to a line between the posterior SCM margin and the posterior anterior scalene muscle	Lower jugular nodes
V	• From skull base to cricoid arch, posterior to posterior margin of SCM (level VA) • From cricoid arch to clavicle, posterior to a line connecting the posterior margin of the SCM with the posterolateral aspect of the anterior scalene (level VB)	Posterior triangle
VI	• Anterior to trapezius • Inferior to hyoid • Superior to top of manubrium	Paratracheal, pretracheal, prelaryngeal, visceral nodes
VII	• Medial to carotid arteries • Inferior to top of manubrium • Superior to innominate vein • Medial to carotid arteries	Upper mediastinal
Supraclavicular	• Lateral to carotids • Level or inferior to clavicle • Superior and medial to ribs	
Retropharyngeal	• Medial to internal carotid arteries • <2 cm from skull base	

Abbreviation: SCM, sternocleidomastoid.

Source: From Ref. 1.

Metabolically active brown adipose tissue, previously felt to be muscular uptake before the advent of PET/CT, may complicate the interpretation of images in the head and neck (13). Although symmetrical in nature, this uptake can mask focal activity in FDG-avid lymph nodes even when the corresponding CT information is available.

MALIGNANCIES OF THE HEAD AND NECK

Head and neck cancers are estimated to affect approximately 34,000 Americans in 2006 (14) and over 7400 Americans died from head and neck cancers in 2006 (14). While head and neck cancers constitute approximately 2%

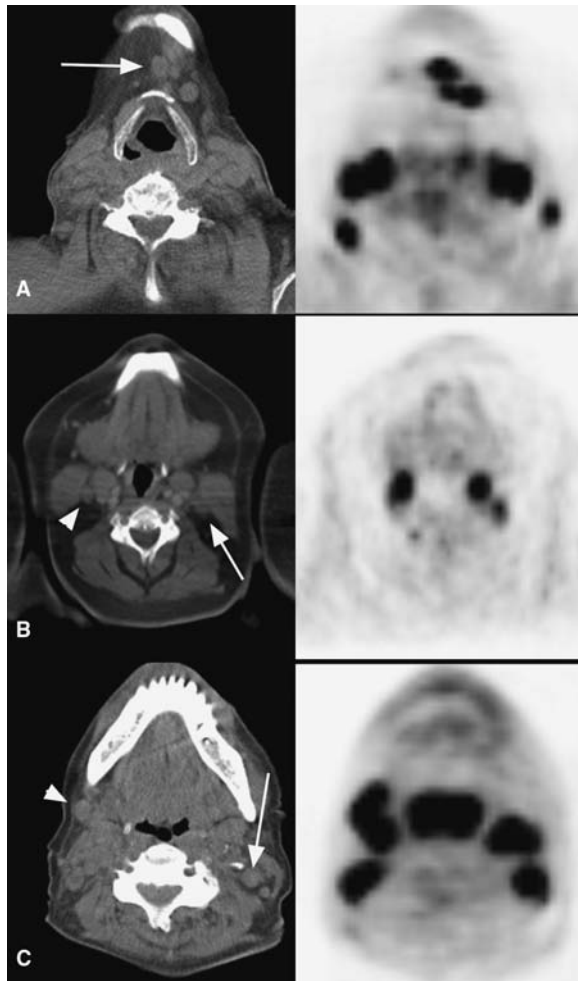


Figure 8 Lymph node levels I. PET/CT in a 53-year-old man with lymphoma and cervical adenopathy. (A) Level IA lymphadenopathy (arrow). (B) Right level IIA lymph node (arrowhead) and left level IIB node (arrow). (C) Right-sided level IB lymph nodes (arrowhead) and bilateral level IIB lymph nodes (arrow on left).

to 3% of all cancers in the United States and are relatively rare, it is the fifth most common malignancy worldwide. Head and neck cancers encompass a diverse group of tumors involving the upper aerodigestive tract including the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. The overwhelming majority of tumors are primarily squamous cell tumors arising from mucosal surfaces especially of the oral cavity, nasopharynx, and larynx. Major risk factors include tobacco and alcohol abuse (15). Both substances are independent risk factors and when combined act synergistically to increase the risk for disease. Other risk factors include betel nut chewing, *Human papillomavirus*, Epstein-Barr virus, gastrointestinal reflux, marijuana use, chronic and excessive use of mouthwash containing alcohol, and poor dental hygiene

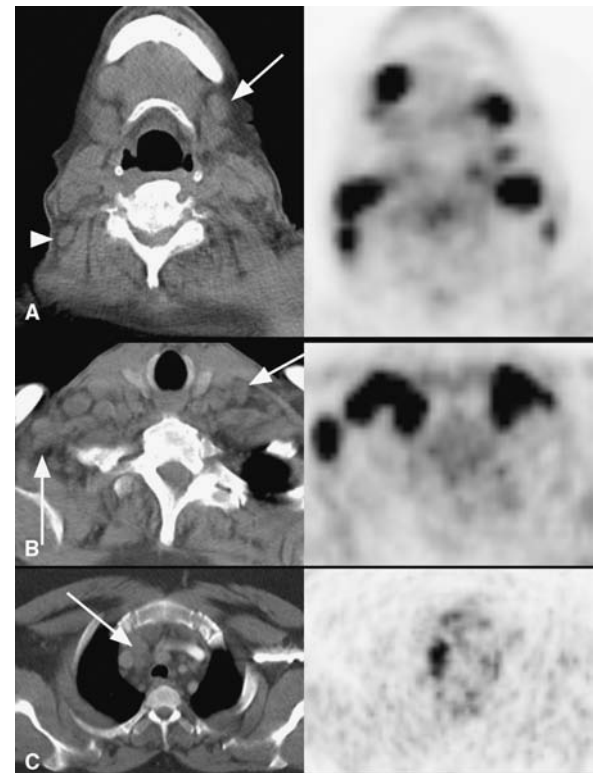


Figure 9 Lymph node levels II. PET/CT in same patient as Figure 8. (A) Bilateral level IB lymph nodes (arrow on left) and right-sided level V lymph node (arrowhead). Level II nodes are also present. (B) Bilateral level IV lymphadenopathy (arrow on left). Right supraclavicular lymph nodes on right (vertical arrow). (C) Level VII lymph node (arrow).

(16,17). Head and neck carcinomas are typically seen in males greater than 50 years of age, but are increasing in frequency among woman and young males (18).

Early detection and accurate staging are essential for treatment and prognosis (19). Nearly two-thirds of patients present with locally or regionally advanced disease (20). Surgery and radiation therapy either alone or in combination with chemotherapy, is used to treat most head and neck cancers. Overall, there is only a 50% five-year survival for head and neck cancer, with an early presentation having a better prognosis regardless of the subsite. The recurrence rate is high, ranging from 23% to 50% in the first year. Despite improvements in diagnosis and management, five-year survival has not improved in part because staging stratification may not be perfected (21). In addition, approximately 17% of patients harbor a second primary squamous cell cancer in the neck or chest (3,4).

CT and MRI, which provide anatomical and structural information, are the standard imaging techniques used for the evaluation of the patient with head and neck

cancer (22). FDG PET depicts cancer sites on the basis of their metabolism and is becoming an increasingly used clinical imaging modality for the detection and localization of head and neck cancers. A focal area of abnormally increased FDG activity is considered suspicious for malignant disease. On the other hand, the determination of malignancy on CT and MRI is based on the tumor morphologic characteristics such as pattern of enhancement and anatomic structural information by demonstrating destruction of normal fascial planes and tumor infiltration into deeper structures (Table 3) (23). In addition, metastases to lymph nodes are characterized by regional lymph node size criteria (24) and morphology, such as central necrosis or irregular margins. Following radical surgery or radiation therapy for head and neck malignancies, there is distortion of normal anatomical tissue planes which results in poor specificity for cross-sectional imaging in the assessment for residual or recurrent tumoral disease. Because PET evaluates tumor metabolism, it is independent of tumor location or size. It has a particularly useful role in the posttreatment interval when it may be difficult to separate scar or radiation changes. One of the major limitations of PET is the lack of anatomic detail. However, this limitation is overcome with combined PET/CT, which permits almost synchronous image acquisition with exact coregistration of anatomic and metabolic data (19). PET/CT imaging is rapidly becoming the favored method as it allows for anatomic localization and increases diagnostic accuracy compared with PET alone. The Center for Medicare and Medicaid Services guidelines now recognizes the use of FDG PET and PET/CT for the diagnosis, staging, and restaging of head and neck cancers (25).

Staging Head and Neck Cancers

Accurate staging is the single most important factor in patient assessment, treatment planning, and determination of prognosis (26). Lymph nodes of the head and neck are considered abnormal if they measure greater than 10 mm in any axial dimension (24). Staging criteria for head and neck cancers have been developed by the AJCC. The stage groupings used for head and neck cancers are based on the anatomic TNM classification: T (primary tumor), N (regional node), and M (distant metastasis). The TNM classification of a tumor derives the anatomic extent of the disease on the basis of the clinical information including imaging. Tumor staging is specific to the site of origin of the tumor because of differences in growth, behavior, and prognosis for each anatomic site, as well as very specific attributes of each anatomic site, but nodal staging criteria and stage grouping are uniform for all head and neck tumors, except for tumors of the nasopharynx (Tables 4 and 5).

Nasopharyngeal Carcinoma

NPC is characterized by local aggressiveness and high rate of regional spread to lymph nodes. Most are undifferentiated carcinomas but adenocarcinoma, cystic adenoid carcinoma, rhabdomyosarcomas, and lymphoma also occur (27). Probably, the most common site of origin is at the fossa of Rosenmüller with infiltration of palatine muscles. Nodal involvement is found in 90% of patients at presentation, often beginning in the retropharyngeal lymph nodes, but sometimes skipping the retropharyngeal nodes and involving high jugular nodes (27). In fact, it has been suggested by some that level II node metastases may be even more common than retropharyngeal metastases with lower incidences of levels III and V and supraclavicular involvement (28). Because initial staging will direct appropriate clinical management, outcomes in terms of overall survival and distant failure are dependent on the accuracy of staging (19,29). Staging for nasopharyngeal tumors is described in Tables 4 and 5.

Tumor staging

Spread superiorly to the skull base is of concern in NPC. Anteriorly, these tumors tend to spread into the nasal fossa and then infiltrate the pterygopalatine fossa (27). Laterally, they may spread into the parapharyngeal spaces and posteriorly into the retropharyngeal space and prevertebral muscles, involving vertebral bodies in very advanced cases (27). Parapharyngeal space extension occurs in a very high percentage of patients (Fig. 10) and its extent may be an independent prognostic factor for overall outcome (30). Submucosal extension may occur inferiorly into the oropharynx and tonsillar fossa. With advanced-enough disease, these directions of spread may cause perineural involvement and even intracranial extension. Distant metastases are seen in 20% to 41% of patients and most commonly affect bone, liver, or lung (27). MRI has become the modality of choice, but PET alone has shown a sensitivity of 93%, a specificity of 100%, and an accuracy of 94% for detection of primary tumors (Fig. 11) (31). PET has shown an advantage over CT because of metal artifacts from the oropharynx on CT; however, with PET/CT these metal artifacts may introduce error into the PET as well (2). Nonetheless, for primary tumors PET/CT has shown an accuracy of 88% compared with 80% for PET alone and 64% for CT (32).

Lymph node staging

Nodal staging has a significant impact on outcome in terms of disease free survival, distant failure and overall survival post therapy (33). CT and MRI are the diagnostic tools most traditionally associated with initial staging, especially for primary tumor assessment. CT and MRI, however, depend upon size criteria and enhancement

Table 3 Possible Signs of Head and Neck Tumor on CT

Nasopharyngeal cancer	Soft tissue mass posterior nasopharynx Involvement of the posterior choana Filling of the nasal cavity Soft tissue filling of the pterygopalatine fossa Soft tissue filling of masticator space Opacification of the mastoid space Para pharyngeal soft tissue thickening and enhancement Soft tissue thickening and enhancement at the pterygoid process Erosion pterygoid process Sclerosis pterygoid process Permeative or erosive skull base bone changes
Oropharyngeal cancer	Contrast enhancement Soft tissue thickening Bulky soft tissue
Late phenomena	Fatty tissue infiltration Bony erosion
Laryngeal cancer	
Supraglottic lesions	
Suprahyoid epiglottic lesions	Thickening and enhancement of the epiglottis Amputation and ulceration of the epiglottic tip Soft tissue filling of the vallecula
Late phenomena	Invasion of tongue base or posterior oropharynx
Infrahyoid epiglottis	Invasion of the preepiglottic space Invasion of valleculae Invasion of tongue base Invasion of epiglottic petiolus
Late phenomena	Anterior commissure thickening Aryepiglottic fold thickening
Aryepiglottic fold tumors	False cord invasion Paraglottic space invasion False cord invasion True cord invasion Cricothyroid joint invasion
False cord tumors	Pyriform sinus filling Invasion of the paraglottic space at the infrahyoid epiglottis/aryepiglottic fold level Invasion at true cord level
Glottic tumors	
Anterior commissure lesions	Thickening of true cords and anterior commissure Extension into the extralaryngeal space; breaching of the cricothyroid membrane
Posterior lesions	Thickening and enhancement of true cord Extension to arytenoids (with sclerosis) and cricoarytenoid cartilage Thickening and filling of paraglottic space
Late phenomena	Laryngocele caused by obstruction of ventricular orifice Laryngeal cartilage sclerosis Erosion of thyroid cartilage
Subglottic tumors	Involvement of esophagus and retropharyngeal space Thickening and enhancement of soft tissue inside the cricoid cartilage Invasion/erosion of the cricoid cartilage Anterior or posterior subglottic soft tissue thickening Invasion of the cricothyroid membrane

Source: From Refs. 77, 121–123.

Table 4 Staging of Nasopharyngeal Tumors

T-staging	
T1	Tumor confined to nasopharynx
T2	Tumor extends to soft tissues of oropharynx and/or nasal fossa
T2a	No parapharyngeal extension
T2b	Parapharyngeal extension present
T3	Tumor invading paranasal sinuses and/or bony structures
T4	Intracranial extension, perineural extension, involvement of the infratemporal fossa, hypopharynx, or orbit
N-staging	
Nx	Nodal involvement unassessable
N0	No regional nodal involvement
N1	Unilateral lymph node involvement above the supraclavicular nodes, ≤ 6 cm in largest dimension
N2	Bilateral lymph node involvement above the supraclavicular nodes, ≤ 6 cm in largest dimension
N3	
N3a	Lymph nodes >6 cm in largest dimension
N3b	Supraclavicular lymph node involvement

Source: From Ref. 83.

Table 5 Staging of Nasopharyngeal Tumors

Stage 0	T in situ	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2a	N1	M0
	T2b	N0, N1	M0
Stage III	T1	N2	M0
	T2a–T2b	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1



Figure 10 CT Nasopharyngeal cancer. Contrast-enhanced CT scan demonstrates a moderately enhancing tumoral mass filling the left nasopharynx (arrow) and extending to the midline and laterally to spread into the parapharyngeal space (ps). Note that the tumoral enhancement is more than would be seen with hypertrophied right adenoidal tissue.

patterns, both of which may underestimate the overall stage. Necrosis and extracapsular extension are further MRI criteria (28). The reported sensitivity, specificity, and accuracy of CT for cervical nodal metastases were 88%, 86%, and 87%, respectively (31) with specificity decreasing to 39% for CT and 48% for MRI when a 10-mm size criterion is applied for lymph nodes (34). The overall diagnostic accuracy of PET/CT in staging of lymph nodes in nasopharyngeal cancer approaches 88% in one series compared with 72% for PET alone and 35% for CT (32).

Staging distant metastases

In addition, because FDG PET images the whole body, it offers the advantage of revealing unexpected tumor foci outside the head-and-neck region with a high sensitivity.

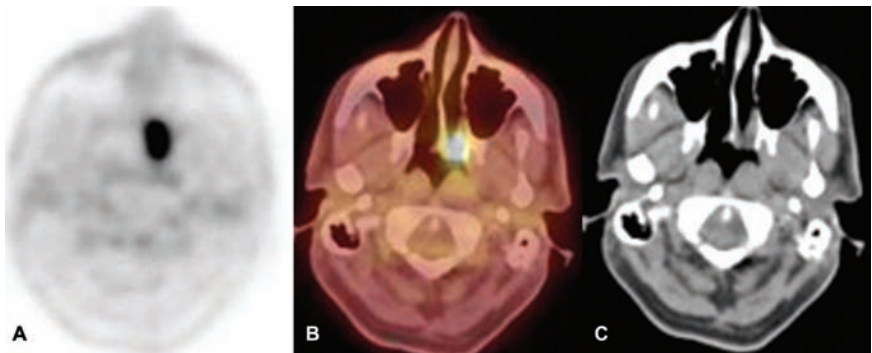


Figure 11 Nasopharyngeal primary PET. FDG avid primary nasopharyngeal squamous cell carcinoma seen on (A) PET (B) fuses to soft-tissue density at the posterior aspect of the left nasal cavity on (C) CT.

Studies have demonstrated the discovery of previously unsuspected distant metastases in 24% of patients, which were correctly defined as such by PET/CT (32). The utility of PET for staging distant metastases is widely acknowledged and particularly recommended for patients with stage T2b or N3 disease (35). In a larger series of patients with nasopharyngeal tumors, FDG PET alone had a 91.6% accuracy and a 63% positive predictive value (PPV) with a significant number of false positives due to muscle and inflammatory tissue, particularly tuberculous lesions (36). However, this accuracy was higher than that of CT. In another series, PET alone showed a 92% sensitivity. The incidence of distant metastases rose to 56% of patients with the more advanced N2 and N3 diseases (36,37). T-stage did not appear to relate to the incidence of distant metastases (36).

Recurrent and residual nasopharyngeal tumor

PET/CT is advantageous in the detection of recurrent or residual disease in patients with NPC as well as in restaging early in therapy. Since the primary treatment for this cancer involves radiation therapy, morphologic imaging modalities are limited in posttherapy evaluation by fibrotic changes, which alter tissue appearance and may obscure residual or recurrent disease. Overall, metabolic imaging with FDG is superior to CT and MRI in detecting recurrent or residual NPC (38). CT has shown a moderately high (78%) PPV for recurrence but a low negative predictive value (NPV) in the previously irradiated patient (39). MRI has shown similar sensitivity to PET in detecting recurrence, but lower specificity (40). Only in patients treated with brachytherapy did PET lack specificity. Finally, in a study of patients with equivocal MRI findings, FDG PET has shown a high 91.6% sensitivity and a 76.0% specificity for local recurrence, 90% sensitivity and 88.9% specificity for nodal recurrence, and 100% sensitivity and 90.6% specificity for distant recurrence (41).

Depending on the time interval between the most recently administered radiation therapy and the PET/CT scan, standardized uptake values (SUVs) may or may not be useful in distinguishing benign from malignant disease. In general, the shorter the time interval, the greater the likelihood that the higher SUV will indicate a false-positive secondary to increased metabolic activity of posttherapy inflammatory type changes. A survey of the literature demonstrates a wide range of time intervals for follow-up scan, from six weeks to four months, but the overall consensus is that the longer the time interval, the greater the confidence that an increased SUV is, in fact, suspicious for malignancy. Recently, an SUV of less than 4.0 at three months after completion of therapy predicted a good response (42) as did a cutoff of 4.2 in another study at the same time point (40). Another group assessed patients at greater than eight weeks after the conclusion of radiotherapy and found a greater accuracy for PET/CT

than for the contrast-enhanced CT portion alone. Sensitivity and specificity for PET/CT were 76.9% and 93.3%, respectively, compared with 92.3% sensitivity and 46.7% specificity for CT alone (43).

Restaging by FDG PET after the first or second course of induction chemotherapy is also important in predicting response and outcome in patients with locoregionally advanced NPC and has advantages over conventional imaging (44). Patients who fail to demonstrate an appreciable decrease in metabolic activity following induction chemotherapy may be identified earlier and subsequently undergo a change in treatment, avoiding potentially ineffective chemotherapy (45). FDG PET was also found to have an impact on the decision to proceed with salvage treatment for locally persistent NPC by identifying patients who were not likely to benefit from additional treatment and by improving accuracy of gross tumor volume definition in salvage treatment planning (46).

Oral Cavity and Oropharyngeal Cancer

Approximately 30% to 50% of all head and neck malignancies are oral cavity cancers, and the overwhelming majority of these, on the order of 95%, are squamous cell carcinoma (SCC) (18,47). However, adenoid cystic tumors and tumors of the minor salivary glands also occur, as do lymphoma and melanoma (47). Tumors of the oropharynx tend to have a different pattern of spread than those originating in the oral cavity (47). The oropharynx encompasses the base of the tongue, soft palate, and palatine tonsils. The oral cavity includes the oral tongue, floor of the mouth, hard palate, the upper and lower alveolus, the buccal mucosa, and the retromolar trigone. Usually these tumors are diagnosed on physical examination so that, more often, the role of imaging is to assess local extent as well as lymph node and distant metastases. Also, since squamous cell tumors are associated with synchronous primaries of the aerodigestive tract, patients should be screened for these as well (48).

Staging of oral and oropharyngeal cancers

CT and MRI are standard modalities for staging. On CT, squamous cell cancer tends to enhance only slightly (47) but is particularly useful in assessing bone invasion. MRI, similarly, will be useful in detecting direct marrow invasion, for evaluation of hard palate tumors and for detecting perineural invasion (47). At the time of diagnosis, 50% of patients have locoregional disease and 10% have distant metastases (47,49).

Primary oral cavity tumor staging

The local extent of tumor dictates clinical management (Fig. 12). Primary tumor staging for oral cavity cancers is described in Table 6. Tumor thickness that is best assessed

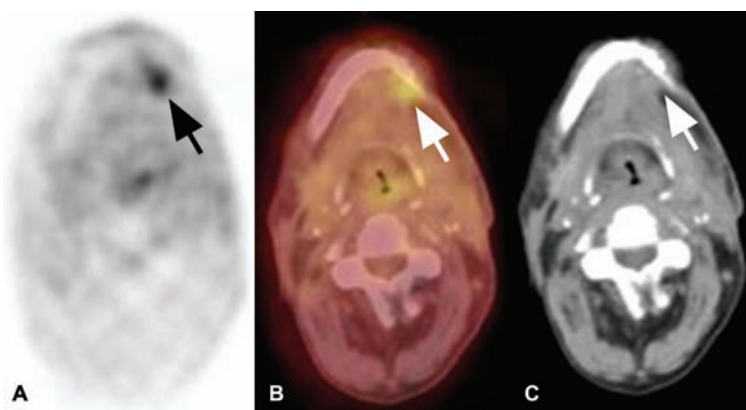


Figure 12 Oral cavity primary. FDG avid focus (arrow) on (A) PET in the left floor of mouth adjacent to the alveolar ridge (B) fuses to a small soft-tissue density (arrow) on (C) CT. Biopsy revealed a squamous cell carcinoma.

Table 6 TNM Staging of Oral Cavity and Oropharyngeal Cancers

Tumor staging	
TX	Primary tumor unassessable
T0	No primary tumor evident
Tis	Carcinoma in situ
T1	Tumor, ≤ 2 cm in greatest dimension
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension
T3	Tumor > 4 cm in greatest dimension
T4a	
Lip	Tumor invades into cortical bone, inferior alveolar nerve, floor of mouth, or skin of face
Oral cavity	Tumor invades through cortical bone, into deep muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or the skin of face
T4b	Tumor extends into the masticator space, pterygoid plates, or skull base or encases internal carotid artery
Lymph node staging	
Nx	Regional lymph nodes unassessable
N0	No regional lymph node metastasis
N1	Metastasis in a one ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2	
N2a	Metastasis in one ipsilateral lymph node > 3 cm but not ≤ 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none ≤ 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph > 6 cm in greatest dimension

Source: From Ref. 83.

by contrast-enhanced CT or by noncontrast and gadolinium-enhanced MRI relates to overall survival in these patients (50,51). It is important to determine if the midline fibrofatty septum of the tongue is involved in oral tongue cancers and also if there is extension to the base of the tongue in determining clinical management. Tumors of the retromolar trigone may invade the mandible because of their close proximity; and perineural invasion is more common with these and also with hard palate tumors (47).

Lymph node staging

The presence of nodal metastases in patients with these tumors carries prognostic significance and extracapsular spread worsens that prognosis even further (52). Tumors of the hard palate and upper alveolus are less likely to produce lymph node metastases than tumors of the tongue or the floor of the mouth since the latter areas are richer in lymphatics (47). The TNM system for assigning nodal stage is described in Table 6. In these tumors, CT is more sensitive than MRI for demonstrating both extracapsular spread manifested by stranding on CT and necrosis in lymph nodes. Uniform enhancement on CT may also be present. Although the role of FDG PET in staging oral cancer is somewhat controversial, in one study, FDG PET was more sensitive than CT/MRI for detecting cervical nodal metastasis of oral cavity SCC patients with a sensitivity of 88% and a specificity of 93% (53). False positives, such as inflammation or infection, as well as false negatives, as in disease less than 5 mm, remain relative limitations to this modality. FDG PET showed a slight increase in the AUC of receiver operating curves over CT and MRI in staging cervical lymph nodes in another series of patients with buccal mucosa tumors without clinical evidence of distant metastases. In this subset of patients, PET led to avoidance of unnecessary surgery in one of 51 patients (54). In a report by Goerres et al, FDG PET served to upstage the N-stage in a small

number of patients (55) and led to management changes. In a comparison of PET with ultrasound, CT, and MRI, ultrasound was more sensitive for cervical lymph node metastases, but PET had the highest specificity (56). In the patient with oral cavity cancer who has a clinically negative neck, FDG PET has not been proven to adequately replace supraomohyoid neck dissection for staging, primarily because of the limits of resolution of the camera and the inability to detect micrometastatic disease (57). Although dedicated CT and MRI are less sensitive than PET, morphologic imaging is still necessary for adequate surgical planning.

Distant metastatic disease

The incidence of distant metastases is probably slightly lower in oral cavity SCC than carcinomas from other sites of the head and neck (58), but patients with evidence of enlarged contralateral lymph nodes or with evidence of extranodal spread on MRI are at increased risk for distant metastases (59). These patients in particular may benefit from whole body PET/CT. Metastases have been described in lung, liver, mediastinum, colon, and bone (55,60,61). Because of detection of distant metastases (56), PET can change treatment plans in these patients (55). Melanoma of the oral cavity is more likely to metastasize than the squamous cell cancers and FDG PET will be exquisitely sensitive for the detection of these metastases (62).

Staging of oropharyngeal cancers

Oropharyngeal cancers have a high rate of locoregional spread and higher overall likelihood of metastatic involvement than that of even oral cavity SCC. There is also increased morbidity associated with surgical resection. As such, accurate initial staging is vital in treatment decision

making. At the time of presentation 45% to 78% of patients with oropharyngeal primary malignancy may have cervical lymphadenopathy (necrotic nodes from oropharyngeal SCC) (63). Again, morphologic imaging modalities, CT and MRI, face the challenges in accurate initial staging discussed previously, and in oropharyngeal carcinoma have a reported sensitivity of 36% to 94% and specificity of 50% to 98% (63).

T-staging and detection of primary oropharyngeal cancers

PET has demonstrated a higher sensitivity than CT or MRI in the detection of primary oropharyngeal tumors (Fig. 13) (51), although tonsillar tumors may be an exception even with PET/CT (12). Also, multivariate analysis indicates that high FDG uptake is an independent prognostic factor in oropharyngeal cancer (64).

Lymph node staging of oropharyngeal cancers

FDG-PET is more sensitive (97%) in the detection of neck metastases than CT/MRI (76%), with comparable specificity (90%). Metabolic imaging is also more sensitive in the detection of positive cervical levels (96%) versus CT/MRI (79%), again with comparable specificity (86–87%) (53). The PPV of PET for lymph node level was only 74%, making it an insufficient replacement for histologic sampling (53). In the staging of oropharyngeal carcinoma, the PPV of PET and CT/MRI were similar (96%), but the NPV of PET was higher (90%) in comparison with conventional imaging (56%) (53). In another series of patients with oropharyngeal cancer who were clinically staged as N0, PET had a slightly lower sensitivity for cervical lymph node metastases than CT (65). It has been suggested that while PET may lack the sensitivity for micrometastases (66), a negative FDG PET can be used to select patients for sentinel lymph node identification and biopsy (65). As in oral cavity SCC, the diagnostic accuracy of

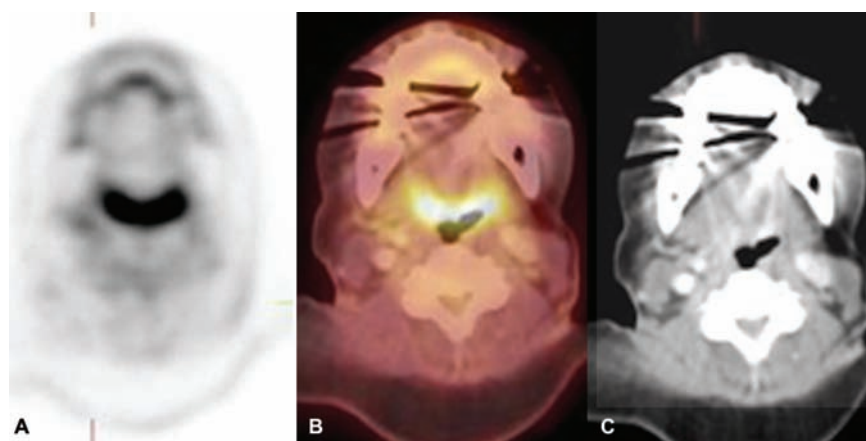


Figure 13 Base of tongue. Increased radiopharmaceutical uptake on (A) PET (B) fuses to the asymmetric soft tissue fullness at the right tongue base on the (C) CT. Note that the PET activity crosses the midline consistent with the biopsies that showed bilateral squamous cell carcinoma.

PET is important in pre-operative staging, but cannot replace staging by pathology.

Distant metastases in oropharyngeal cancer

The overall incidence of distant metastatic disease in patients with oropharyngeal cancers was about 10% in a large series of patients (67), but is even lower at presentation of disease (68). Like all head and neck cancers, adequate treatment to affect local control decreases the incidence of distant metastatic disease (67,69). As in oral cancer, the presence of perineural invasion is a risk factor for distant metastases (70) as is extracapsular extension of nodal metastases (71). These are the patients who will most benefit from PET assessment (59).

Recurrent oral and oropharyngeal cancers

The rate of recurrence of these tumors is related both to initial clinical stage and to adequacy of initial treatment (72). The five-year cumulative local control rate in a series of T2–T4 tumors was approximately 80%. Combined modality therapies appear to be the most effective in reducing recurrence (73). Detection of recurrence in oral cavity and oropharyngeal cancer is difficult using conventional imaging secondary to radiation fibrosis and scarring. Although PET also has limitations secondary to false positives, the high sensitivity (100%) and NPV (100%) in one series (74) and 94% sensitivity for local recurrence in another (75) are very useful in the early detection of recurrence, both locoregional and distant, and in the confirmation of absence of significant viable tumor (51). PET alone has shown a high sensitivity but only moderate specificity (64%) for primary site recurrence, with better specificity (77%) and high sensitivity for nodal recurrence (76). Although minimal disease presents a limitation for PET (75), PET has been shown to have a high NPV for recurrent disease (76).

Hypopharyngeal and Laryngeal Cancer

Laryngeal cancer is the most common site of head and neck primary tumors with tumors of the larynx exceeding hypopharyngeal tumors by about 4:1 (77). Most are SCC, but adenoid cystic carcinoma, carcinosarcoma, leiomyosarcoma, rhabdomyoma, and chondrosarcoma have all been reported (77–81). The SUV of the primary tumor (>9) has been shown to predict local recurrence in patients treated with radiation with or without chemotherapy regardless of T-stage (64) and to correlate with histologic grade (82).

Primary hypopharyngeal and laryngeal tumor staging

Although most laryngeal tumors are mucosal, and therefore easily seen on endoscopy, it is important to accurately assess submucosal extension. The staging of laryngeal

Table 7 T-Staging of Laryngeal Cancers by Location

Supraglottic tumors	
T1	One site of supraglottic tumor with intact vocal cord mobility
T2	Tumor invasion of mucosa at more than one adjacent site in the supraglottis, glottis; no fixation of the larynx
T3	Vocal cord fixed; invasion of the postcricoid region, preepiglottic or paraglottic space or minor thyroid cartilage involvement
T4	Extra laryngeal tumor extension
T4a	Invasion of thyroid cartilage or other perilaryngeal tissues, such as trachea, muscles, esophagus)
T4b	Invasion of the prevertebral space, the mediastinum, or encasement of the carotid artery
Glottic tumors	
T1	Tumor confined to vocal cord
T1a	Tumor involving one vocal cord
T1b	Tumor involving both cords
T2	Extension into supraglottis and/or subglottis, and/or impaired vocal cord mobility
T3	Fixed vocal cord; invasion of paraglottic space; minor thyroid cartilage erosion
T4	Extralaryngeal extension of tumor
T4a	Invasion of thyroid cartilage or other perilaryngeal tissues, such as trachea, muscles, esophagus)
T4b	Invasion of the prevertebral space, the mediastinum, or encasement of the carotid artery
Subglottic tumors	
T1	Tumor confined to subglottis
T2	Tumor extension to vocal cords with normal to impaired mobility
T3	Fixation of cords
T4	Extralaryngeal extension of tumor
T4a	Invasion of thyroid cartilage or other perilaryngeal tissues, such as trachea, muscles, esophagus)
T4b	Invasion of the prevertebral space, the mediastinum, or encasement of the carotid artery

Source: From Ref. 83.

tumors depends on whether they are glottic, supraglottic, or subglottic (Table 7) (83). Hypopharyngeal tumors tend to be more infiltrative and carry a somewhat worse prognosis (Fig. 14) (77). T-staging for hypopharyngeal tumors is also site specific (77,83) (Table 8). Tumor volume greater than 6 mL as estimated by CT and extension into the laryngeal cartilage appear to be the best predictors of local control in response to radiotherapy alone (77). In general, contrast-enhanced CT will provide adequate

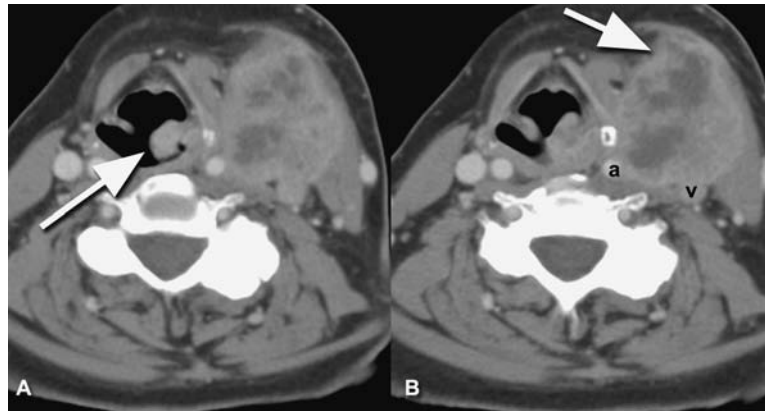


Figure 14 CT hypopharynx mass. (A) Left pyriform sinus tumoral mass (*arrow*) with “C-shaped” appearance with (B) necrotic conglomerate level III adenopathy (*arrow*) with loss of the tissue plane behind the left sternocleidomastoid muscle and abutting the left carotid artery (a) and displacing the left jugular vein (v).

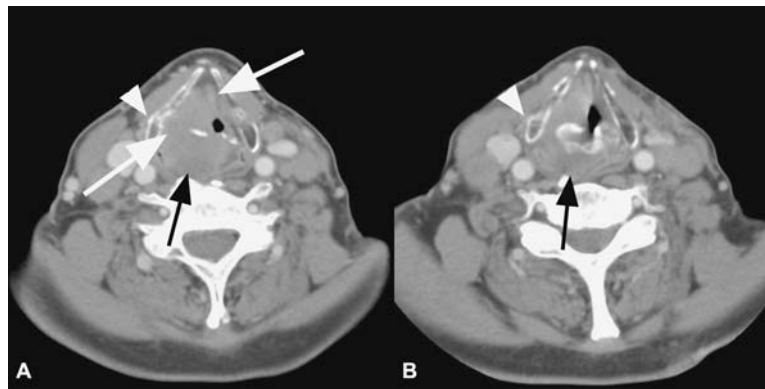


Figure 15 CT laryngeal cancer. Right true vocal cord mass with widening of the (A) thyroarytenoid space (*white arrows*) and (A and B) extension to the postcricoid region (*black arrows*). Also note sclerosis of the right thyroid cartilage (*arrowheads*), which is nonspecific. Multiple bilateral level III lymph nodes are present.

information for primary tumor staging (Fig. 15), but MRI provides a better assessment of cartilage invasion (84). PET alone has proved sensitive in detection of tumors, but is plagued by false positive uptake at the larynx (56).

Lymph node staging of hypopharyngeal and laryngeal tumors

Criteria for staging of lymph nodes in laryngeal tumors is described in Table 9 (83). On CT, as with other head and

neck cancers, enlargement of lymph nodes to 15 mm or more for upper jugular nodes and submandibular lymph nodes, to 10 mm or more for other cervical nodes, and central hypodensity suggesting necrosis suggest lymph node metastases (Fig. 14) (77,85). In laryngeal cancer, CT has shown a sensitivity of 90% with a specificity of 73% (77). In another series, FDG PET had similar accuracy to CT, both of which were better than physical examination (85). In another very small series of 12 patients, PET showed a similar sensitivity to MRI (86).

Table 8 T-Staging of Hypopharyngeal Tumors

Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in largest dimension and limited to one subsite within the hypopharynx: pyriform sinus, posterior hypopharyngeal wall, or postcricoid region
T2	Tumor invading more than one subsite of the hypopharynx or >2 cm and ≤ 4 cm in largest dimension, but no fixation of the hemilarynx
T3	>4 cm in largest dimension or fixation of hemilarynx
T4	Tumor invading adjacent structures

Source: From Ref. 83.

Distant metastases from hypopharyngeal and laryngeal tumors

The most common site of metastases is the lungs, with liver and bone the next most frequent. When liver or bone metastases are present, lung metastases are also likely present (87). Screening for distant metastases at presentation probably should be reserved for locally advanced disease, N2 or N3 disease, extracapsular extension of lymph node involvement, perineural invasion, adenoid cystic or poorly differentiated tumors, and hypopharyngeal tumors as well as

Table 9 Nodal Staging of Laryngeal Tumors

Lymph node staging	
Nx	Regional lymph nodes unassessable
N0	No regional lymph node metastasis
N1	Metastasis in a one ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2	
N2a	Metastasis in one ipsilateral lymph node >3 cm but not ≤ 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none ≤ 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph >6 cm in greatest dimension

Source: From Ref. 83.

in the setting of local recurrence (Fig. 16) (87,88). Chest CT and probably FDG PET are both indicated in these high risk settings (77). In line PET/CT has not been examined in this setting.

Recurrent laryngeal cancer

Detection of recurrence in the post radiation setting can be problematic, with direct biopsy probably the most common procedure undertaken, but biopsy may contribute to edema and even infection, complicating the symptoms and imaging appearance of the affected area (89). Overall in laryngeal cancer, PET demonstrates greater accuracy than CT or MRI in the differentiation of recurrent malignancy from postradiation sequelae-like edema (85% vs. 42% in one series and 79% vs. 43% in another) (85,90) and will show involvement of regional nodes that CT might miss (91). Metabolic imaging with FDG is the most sensitive noninvasive modality currently available for differentiating radiation fibrosis and inflammation from active residual or recurrent disease with greater than 90% sensitivity (82,85,92–94). Even with lower sensitivities for PET (80%), metabolic imaging outperformed CT or augmented the information on CT examination in patients with recurrent disease (95). Nonetheless, because of persistent uptake secondary to radiation-induced inflammation, PET lacks specificity and may have a poor PPV (74,92,96). The NPV, however, is high (92,96,97) and negative PET studies will predict the absence of locoregional recurrence and possibly avoid the need to perform neck dissections (96). As with other head and neck tumors, a four-month interval between the cessation of radiotherapy and evaluation provides the best specificity (98,99). Continued decrease in SUV over multiple PET studies is an indicator of response in the setting of prior and relatively recent radiation (74,92). C-11 Tyrosine PET has shown high accuracy in a very limited number of patients (100).

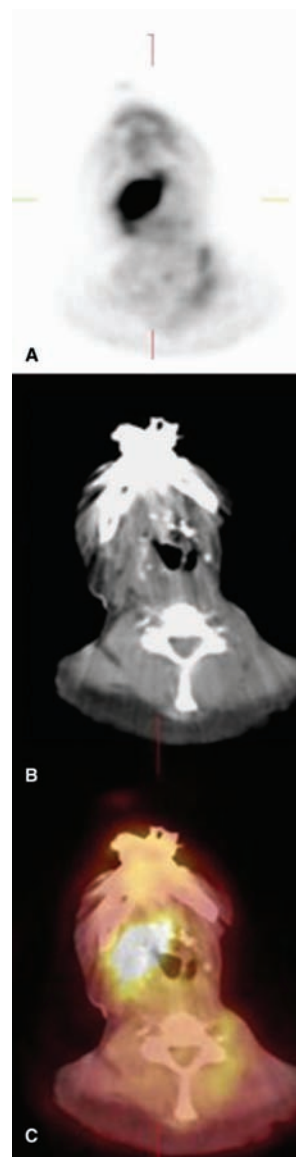


Figure 16 Recurrent squamous cell carcinoma in the right hypopharynx in a patient with a history of left radical neck dissection for laryngeal carcinoma. Marked activity on the FDG PET (A) and a soft-tissue mass distorting the central airway and filling the right pyriform sinus on CT (B) fuse together (C) to demonstrate a large recurrence.

Unknown Primary Tumors

Most carcinomas of unknown primary that present with cervical lymph node metastases are SCCs (101) but adenocarcinomas, melanoma, and other tumors occur as well (102). SCC cervical nodal metastasis from an unknown head and neck primary cancer site accounts for approximately 0.5% to 10% of all squamous cell cancers in the neck and neck (103). Even though the

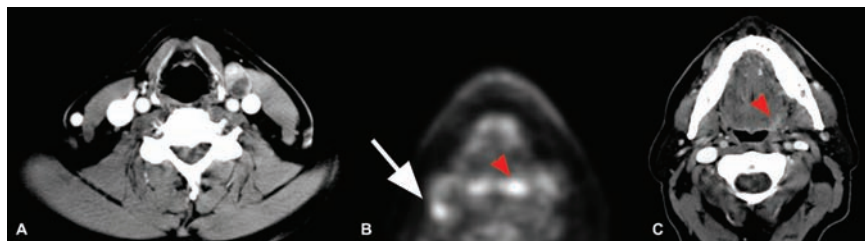


Figure 17 Carcinoma of unknown primary. Patient had a history of Non-Hodgkin's lymphoma stage III treated with CHOP for eight months with remission. Three subsequent follow-up PET scans were negative. The patient then presented with a new left neck mass (A), sore throat, and odynophagia originally thought to be reoccurrence of lymphoma. A biopsy of the left level III lymph node showed squamous cell cancer. (B) PET scan showed uptake in a small focus at the left base of the tongue (red arrowhead) also suggested on the contrast-enhanced CT in retrospect (C) (red arrowhead). (B) PET also showed uptake in a right sided level II lymph node (arrow).

primary remains obscure in the vast majority of cases, curative intent therapy combining surgery, radiation and sometimes chemotherapy may be employed with five-year survival rates in the 40% to 79% range (101,104). However, some still maintain that identification of the primary site will permit improved therapeutic efficacy (105). In 5% to 80% of these cases, depending on the series, the primary tumor cannot be identified by physical examination, panendoscopy or conventional imaging with CT or MRI (101,103). The most common subsites for occult primary tumors are the tonsillar fossa and base of tongue, and has even been reported in a tonsillar remnant after tonsillectomy (106). Other subsites include the pyriform sinus and nasopharynx. The site of a lymph node metastasis, however, may also give a clue as to where the primary tumor may be (33). For example, a level II metastatic lymph node may be the initial presentation of a tonsillar fossa squamous cell cancer.

The relatively high sensitivity of FDG PET for squamous cell cancers of the head and neck, in general, make it a potentially useful tool in identifying the primary site (107). FDG PET is now an acknowledged part of the evaluation of the patient with carcinoma of unknown primary and PET/CT has increased the success rate slightly in identifying the primary site (Fig. 17) (105). PET alone showed utility in the detection of unknown

primary cancers with a sensitivity of 31% in one series where conventional imaging failed (108), 25% in another series (109), as high as 69% in a series covering 1987–2002 (110), and an overall sensitivity in a meta-analysis of 88% but a sensitivity of only 27% when conventional evaluation was negative (111). Comparing PET/CT with PET, CT and side-by-side comparison of PET and CT in a series of 46 patients with carcinoma of unknown primary, Gutzeit et al., in the early phases of PET/CT, found no significant improvement in detection rates by in-line PET/CT over any of the other individual modalities, this time with a detection rate of 33% (112). In another series, the sensitivity of PET/CT for identifying the primary tumor was higher but no different than PET. In this group of patients, PET and PET/CT were almost twice as sensitive as CT (113). A negative PET does not preclude the need for panendoscopy, biopsies, or tonsillectomy in these patients (108).

FDG PET has shown utility in diagnosing distant metastases in patients with unknown primaries, thereby avoiding aggressive locoregional therapy without systemic therapy (102,114–116). On the other hand, it appears that conventional modalities add little to the information from PET/CT (117).

In fact, it has recently been suggested that the primary role of FDG PET or PET/CT is to provide more complete

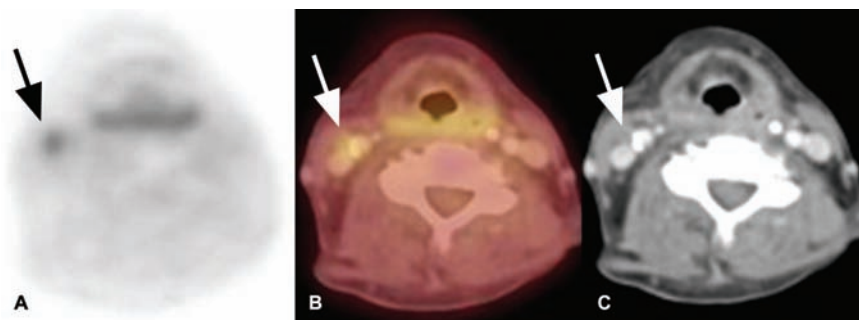


Figure 18 Lymph node staging in carcinoma of unknown primary. FDG avid right level III lymph node in a patient who presented with a 2-cm right-sided level IB lymph node (not shown) and staged as T0 N2b M0 squamous cell carcinoma of the right neck. (A) PET shows mild activity (B) fusing to a small lymph node (arrows) seen on (C) CT.

staging of disease in order to allow more precise tailoring of therapy, and that it can substitute for conventional imaging (Fig. 18) (118). Since identification of the primary tumor has shown no influence on survival and especially because the N stage of carcinoma of unknown primary influences survival (Fig. 17) (119), adequate staging of lymphadenopathy with PET or PET/CT adds value (116). The additional information provided by FDG PET studies led to a treatment modification in about a quarter of patients studied in another series by Johansen et al. (120). Meta-analysis of these studies has shown a similar impact of PET on management (111).

SUMMARY

Knowledge of CT anatomy of the head and neck is critical to interpreting PET/CT in patients with known or suspected head and neck cancers. Use of lymph node levels to describe involvement is particularly important in directing biopsy as well as in proper staging of tumors. Staging of tumors (T-staging) is specific to the site of origin, but lymph node staging is uniform across the head and neck sites.

NPCs have a high incidence of lymph node metastases, usually to either the retropharyngeal nodes or the level II nodes. PET and PET/CT have shown good sensitivity for staging of lymph nodes and metastases as well as detection of primary tumors. This modality plays an important role in predicting response to chemotherapy in patients with these tumors and can be helpful in assessing recurrence, even in patients treated with radiation. For irradiated patients, a three to four-month wait prior to restaging is preferred.

FDG PET has a high sensitivity for oral and oropharyngeal cancers, but may lack sensitivity in detection of tonsillar primary tumors. PET may have insufficient sensitivity for nodal metastases in these tumors, but a positive PET may obviate the need for sentinel lymph node biopsy, while a negative PET may indicate the need for that procedure especially in early tumors. While oral cancers have a low rate of distant metastatic disease, oropharyngeal cancers have a greater likelihood of metastasizing. PET has also shown utility in detection of recurrences.

Laryngeal tumors, which are usually squamous, are characterized as supraglottic, glottic, or subglottic with tumor-staging specific to each of these. PET has been useful in lymph node staging, detection of distant metastases, and detection of synchronous primary tumors. SUV of the primary tumor may offer prognostic information. PET has been useful in distinguishing the sequelae of radiation therapy from recurrence as well as finding regional failures. Hypopharyngeal tumors also have their own tumor-staging system. They are more infiltrative than laryngeal tumors and carry a worse prognosis.

In carcinoma of unknown primary, PET or PET/CT may detect primary tumors that are not otherwise identified by other modalities, but a more important and clinically effective role is to identify distant metastases and to stage lymphadenopathy, as more advanced nodal staging will influence treatment and outcomes.

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6

PET and PET/CT of Thyroid Disease

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INTRODUCTION

Nuclear medicine physicians and radiologists are already familiar with the use of conventional imaging in the management of patients with benign thyroid disease. Diagnosis, follow-up, and therapy for patients with Graves' disease, thyroiditis, thyroid nodules, ectopic thyroid tissue, and other less common conditions has been advanced by myriad imaging modalities including iodine scintigraphy, ultrasound, and in some cases computed tomography (CT) and magnetic resonance imaging (MRI). In recent years, positron emission tomography (PET) and PET/CT have emerged as useful tools for the evaluation of thyroid cancer and have also contributed to the study of the pathophysiology of benign thyroid disease. This chapter will review the utility of PET and PET/CT in the evaluation of patients with both benign and malignant thyroid disorders. A brief review of conventional imaging with a focus on CT will complement the text covering the use of PET.

EPIDEMIOLOGY OF THYROID DISEASE

Benign diseases of the thyroid are very common. Iodine deficiency goiter is the most common worldwide thyroid

disease. Graves' disease occurs with an incidence of 30–200 cases per 100,000/yr, and is 8 times more common in women than men. Hashimoto's thyroiditis (the most common cause of hypothyroidism) is diagnosed in 30–150 individuals per 100,000/yr (1) and may be even more prevalent but underdiagnosed. Multinodular goiter and single nodules are commonly identified on physical exam and found even more commonly during imaging for nonthyroid problems as incidental findings. These incidental findings represent another significant diagnostic and management problem to nuclear physicians, radiologists, and clinicians. The vast majority of thyroid nodules are benign, and the challenge remains to identify the clinically significant thyroid cancer within a large pool of benign lesions.

The American Cancer Society estimated an incidence of 33,330 new thyroid cancer cases in the U.S.A. for 2007 (25,480 females and 8,070 males). They predicted that there would be 1,530 deaths (650 males, 880 females) from this disease (2). Thyroid cancer is the seventh most common type of cancer in women. Although deaths are relatively rare, recurrent disease is common, and thyroid cancer represents a significant challenge to the medical community both with respect to number of patients, cost of care, and most importantly, patient morbidity.

CONVENTIONAL IMAGING AND THYROID DISEASE

Ultrasound and MRI of the Thyroid

There is now a large body of literature discussing the role of ultrasound in the evaluation of thyroid nodules (Table 1). Several authors have proposed various ultrasonographic findings associated with malignancy, including hypoechogenicity, indistinct margins, spherical shape, central hypervascularity, and an incomplete halo (3). None of these features have been proven to be sufficiently specific or sensitive to allow definitive management of thyroid lesions without further evaluation by fine needle aspiration (FNA) biopsy. Ultimately, there is only one ultrasonographic finding that is highly specific for thyroid cancer (finely stippled calcifications), and unfortunately this feature is only seen in 25% of thyroid cancers. A recent consensus conference issued recommendations regarding when to select a nodule for FNA biopsy on the basis of ultrasound appearance, but acknowledged that more work needed to be done to better classify and guide management of thyroid nodules (4).

Others have investigated MRI as a potential tool for evaluation of the thyroid (Table 1). This technique has the advantage of avoiding iodinated contrast, which is discouraged in patients being evaluated for thyroid cancer who may need subsequent treatment with radioactive iodine. In 1990, Eisenberg demonstrated that MRI could not differentiate between benign and malignant thyroid nodules (5). In contrast, in 1995, Lean demonstrated the potential utility of magnetic resonance spectroscopy for characterization of follicular neoplasms (6). In 1999, Wang demonstrated the accuracy of MRI in the evaluation of medullary thyroid cancer (MTC). Primary tumors were detected with 90% sensitivity, and local nodal metastases were diagnosed with 74% sensitivity and 98% specificity (7). The same group also found that MRI can be accurate for the evaluation of esophageal invasion (82% sensitivity, 94% specificity) (8), and thus justifies the potential use of this technique in advanced cases of primary or recurrent

thyroid cancer. Gross et al. found MRI to be highly sensitive (95%) for the detection of cervical metastases but only 51% specific. Features diagnostic of malignancy included minimal axial diameter greater than 10 mm or lesions of any size with increased T2 signal intensity, cystic component, or compression of adjacent structures. (9) In summary, MRI may play a role in staging or restaging patients with advanced thyroid cancer and in the evaluation of large benign goiters, particularly in individuals who require evaluation of the thoracic inlet and mediastinum. It is not currently recommended for routine evaluation of patients with newly diagnosed thyroid cancer or limited recurrent disease.

CT of the Thyroid

Iodinated contrast agents should be avoided whenever possible when CT is used to evaluate thyroid problems, and in any person whose thyroid condition could be complicated by iodine. For instance, in some patients, iodinated dye could cause hyperthyroidism, and thus decompensate a cardiac condition or cause angina or myocardial infarction.

In 1984, Blum and Reede explored the potential utility of CT in managing disease of the thyroid. They found it useful in "the evaluation of cryptic symptoms or structures in the neck after surgery for thyroid cancer, the assessment of the extent of thyroid cancer, the localization of aberrant thyroid tissue, the etiology of unexplained recurrent laryngeal nerve paralysis, and the identification and delineation of mediastinal goiter" (10). There has been a limited amount of additional work examining the utility of CT for thyroid disease, which is summarized below.

Multinodular Goiter

CT is useful for the evaluation of large multinodular goiters. Applications are focused on the ability of CT to precisely define anatomical boundaries, and it is particularly useful for the assessment of displacement or narrowing of the trachea, esophagus, and blood vessels. The CT appearance of a thyroid goiter is characterized by patchy and inhomogeneous density. The gland is often asymmetric with intense enhancement. Hypodense areas and calcifications are often seen corresponding to areas of degeneration (11,12).

Graves' Disease

There is little value in the use of CT for imaging the thyroid in patients with known or suspected Graves' disease, particularly given the accuracy of modern laboratory testing and ultrasonography. Kamijo has described decreased density (as measured by CT Hounsfield units) in the thyroid of patients with Graves' disease compared with normal

Table 1 Ultrasound and MRI Characteristics Suggestive of Thyroid Cancer

Ultrasound	MRI
Hypoechogenicity	>10-mm diameter
Indistinct margins	Increased T2 signal
Spherical shape	Cystic component
Central hypervascularity	Compression of adjacent structures
Incomplete halo	Esophageal invasion
Finely stippled calcification	

controls and found a rise in CT density following therapy with methimazole (13). In general, the utility of CT in Graves' disease is limited. It may have a role in the follow-up of orbitopathy, which manifests as increased retro-orbital fat and increased size of extraocular muscle with sparing of the tendinous insertions (14,15).

Benign Thyroid Lesions

True thyroid cysts are very rare. On CT these lesions have smooth, well-defined borders with thin walls and no calcifications. Thyroid cystic lesions usually result from degeneration of goiters, adenomas, or cancers. Cystic degeneration of an adenoma can vary in density on CT depending on the presence of protein, blood, pus, or serum within the cystic space. Cystic lesions in the neck can be localized to the thyroid on CT by identifying a rim of thyroid tissue at the periphery of the cystic space (12).

Primary Thyroid Cancer

CT is not particularly well suited to the characterization of solitary thyroid nodules detected by palpation, scintigraphy, or ultrasound. In 1984, Radecki et al. compared ultrasound with CT for comparison of thyroid lesions and found that both techniques lacked specificity, and noted that ultrasound was superior to CT for the detection of small nodules (16). Carcinomas of the thyroid can be hypodense, of mixed density, or hyperdense in the setting of hemorrhage or thyroglobulin production. Anaplastic carcinomas are described as large isodense lesions that often contain areas of calcification and necrosis. These features for varying types of thyroid cancer unfortunately overlap with the appearance of benign thyroid nodules. Yao et al. have suggested that well-defined margins and low-density nodular areas on CT suggest benignancy, whereas an irregular border, granular calcifications, complex density, and associated cervical lymph node enlargement are more suggestive of cancer. Diagnostic accuracy was not reported in this study, and it remains to be seen if CT may be of value. The disadvantage of administering IV contrast prior to treating patients who are subsequently diagnosed with cancer and then treated with radioiodine remains a limitation in the use of CT (17). The utility of CT is therefore limited to patients with locally advanced primary tumors in which a surgeon may want to determine the extent of tumor, as it relates to local blood vessel, muscle, fat, tracheal, or esophageal invasion (11). MRI is probably preferred for a patient who may need treatment with radioiodine.

Local Metastases

Fifty percent of patients with papillary thyroid carcinoma are found to have local lymph node metastases at diagnosis (12). Metastatic cervical nodes can vary in appearance from

solid to heterogeneous to cystic and can mimic benign cervical cysts. Metastatic papillary thyroid cancer frequently undergoes cystic degeneration and can mimic metastases from tonsillar and nasopharyngeal carcinomas. Typically, local lymph node metastases are hypervascular and enhance on contrast CT studies. Enhancement can be heterogeneous (18). The accuracy of CT for identifying local metastases has not been determined.

Distant Metastases

Papillary cancer tends to spread locally before the development of distant metastases (most commonly to the lung), but follicular carcinomas are more likely to manifest early involvement of local blood vessels and hematogenous spread to distant sites, commonly the lungs and bones. MTCs are also likely to spread directly to bone, and anaplastic carcinomas are usually locally and widely aggressive (11,12).

Lung metastases manifest two distinct patterns—either diffuse miliary involvement characterized by widespread tiny solid nodules (especially at the lung bases) or a more scattered focal nodular involvement (Fig. 1) (19). Although CT is generally regarded as a highly sensitive modality for detection of early small lung lesions, some authors have suggested that I-131 remains the most sensitive modality for the detection of tiny diffuse lung metastases (20).

Bone metastases are typically lytic and appear as hypodense (Fig. 2), well-circumscribed lesions on CT. Adrenal metastases from papillary thyroid cancer are rare, but have been demonstrated as a large solid mass on CT (21). Round, solid renal metastases of papillary thyroid cancer have also been demonstrated in case reports (22). Abe et al. reported on a heterogeneously enhancing solid renal metastasis of papillary thyroid carcinoma (23). Multiloculated cystic metastases of papillary thyroid cancer in the ovary have been described on MRI and in pathological specimens (24). Cerebral metastases have

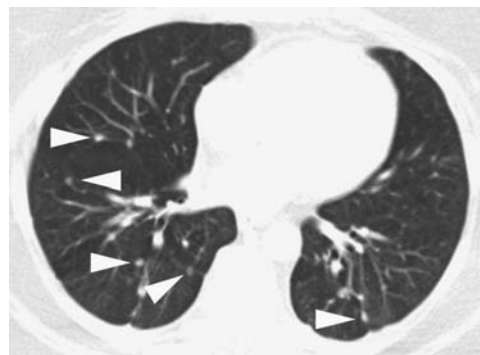


Figure 1 A 57-year-old female with follicular thyroid cancer and lung metastases. CT demonstrates numerous round solid nodules scattered throughout the pulmonary parenchyma.

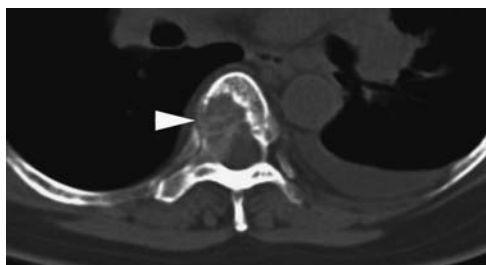


Figure 2 Osseous metastasis. A53-year-old female with a history of metastatic follicular thyroid cancer. CT demonstrates a lytic thoracic vertebral metastasis involving the body and pedicle (*arrowhead*).

been described as ring-enhancing lesions with surrounding hypodensity due to edema (25).

Lymphoma of the Thyroid

Eight percent of thyroid malignancies are due to primary lymphoma. This disease is more common in middle-aged and elderly individuals than in youth. The CT appearance is that of a large homogeneous mass but can be mimicked by Hashimoto's thyroiditis (11).

PET AND PET/CT OF DIFFERENTIATED THYROID CANCER

The study of diseases of the thyroid has been a mainstay of the practice of nuclear medicine since research in this field began after World War II. Radioiodine has played an essential role in the diagnosis, management, and treatment of patients with hyperthyroidism and thyroid cancer. Until recently, gamma camera imaging with ^{123}I or ^{131}I remained the dominant technique for imaging the normal thyroid and thyroid cancer. Now ultrasonography is the initial thyroid imaging modality of choice. With the rising popularity of PET, new techniques now play a vital role in the management of patients with thyroid diseases, and, in particular, thyroid cancer.

Initial Diagnosis of Thyroid Cancer: Evaluation of the Thyroid Nodule

PET has not been tested as a screening tool for thyroid cancer. However, preliminary work has been done in the evaluation of thyroid nodules detected by other means, and several groups have examined the use of PET to differentiate benign and malignant thyroid nodules. In 1993, Bloom and colleagues performed fludeoxyglucose (FDG) PET on 12 patients with solitary thyroid nodules and 7 patients with multinodular goiters who were scheduled for thyroid

surgery. All four malignant nodules demonstrated a maximal standardized uptake value (SUV) of greater than 8.5 and all benign nodules had an SUV of less than 7.6. All multinodular goiters were benign and had an average SUV of 3.0 ± 2.0 (26). The authors concluded that FDG PET could differentiate malignant from benign thyroid lesions discovered by other means. Selection bias could have played a role in that all nodules were scheduled for surgery. Application of this data to the general population of all patients with thyroid nodules is difficult.

In 1988, Uematsu compared the accuracy of ^{201}Tl scintigraphy and FDG PET for the diagnosis of thyroid nodules. When examining 11 patients with nodules varying in size from 1.5 to 5.1 cm, they found all four malignant lesions in this group to have an SUV greater than 5.0 mg/mL and all benign lesions to have an SUV of less than 5.0 mg/mL. One focus of thyroiditis had an SUV of 6.3 mg/mL. The authors concluded that FDG PET could accurately differentiate benign and malignant lesions as long as the scanner resolution was sufficiently high to avoid underestimation of activity by means of partial volume averaging image artifacts. Selection bias in this retrospective study is also of concern. This preliminary study suggested also that FDG PET might be useful in triaging patients with nonspecific nodules (27).

A typical finding in preliminary imaging studies is that reports of high accuracy are followed by studies that demonstrate a degree of lower scan accuracy. The following three investigations concerning FDG PET imaging of thyroid nodules demonstrates a similar trend. In 2003, Kresnik performed FDG PET on 43 patients planning to undergo surgery for thyroid nodules. Using an SUV cutoff of 2.0 the investigators found a sensitivity of 100% for 16 thyroid carcinomas. Specificity was only 63% because of nine false-positive Hurthle cell adenomas. All benign follicular neoplasms had an SUV of less than 2.0. The authors concluded that follicular or Hurthle neoplasms found at FNA could be safely observed if they demonstrated an SUV of 2.0 or less (28). In 2005, Mitchel et al. tested the performance of FDG PET/CT in the preoperative evaluation of thyroid nodules. Thirty-one patients with 48 thyroid lesions found by other means were evaluated. CT images were used to localize thyroid lesions for SUV measurement, but no morphological CT criteria were incorporated into the study. Nine of 15 malignant lesions were classified as malignant using an SUVmax threshold of 5.0, yielding a sensitivity of 60% and a specificity of 91%. Positive predictive value was 75% and the negative predictive value was 83% (29). Despite a disappointing sensitivity, the missed lesions were small papillary cancers that most authorities consider to be of unclear clinical significance. The authors focus on a negative predictive value of 95% for lesions with

indeterminate cytology on FNA, but only one malignant tumor was found in this subpopulation and therefore results of this study are not applicable to a larger population of patients. As the authors state, further studies with larger sample sizes need to be performed. In 2006, de Geus-Oei prospectively evaluated the accuracy of FDG PET in characterizing thyroid nodules with inconclusive FNA biopsy cytology. They found focal thyroid uptake (SUV range 0.9–20.4) in all six carcinomas and in 13 of 38 benign tumors (SUV range 1.1–35.1). Although there was a significant overlap in the SUV range for malignant and benign lesions, they noted that all tumors had at least mild focal uptake and therefore a negative scan effectively ruled out cancer and patients with inconclusive FNA. They suggested that a PET-negative nodule could be safely observed without surgery. Using this management technique, they hypothesized that the percentage of unnecessary thyroidectomies could be reduced from 86% to 30%. The authors recommended against relying on SUV to differentiate benign and malignant lesions. A limitation of this study is that size of the lesions was not reported, and, therefore, it is difficult to determine how to apply this data to very small lesions (30).

In conclusion, emerging data suggests that PET might play a role in the characterization of thyroid nodules. Specifically, a negative PET in the setting of a large nodule might possibly argue for observation instead of immediate surgery. Specificity remains limited (Fig. 3), and sensitivity is not sufficient for the characterization of small nodules. Prospective trials with high performance scanners potentially might lead to a more productive role for PET in future. For now, ultrasound and FNA biopsy are likely to remain the best and most cost-effective modalities for triage of thyroid nodules.

Initial Staging of Thyroid Cancer with PET and PET/CT

Once a thyroid cancer has been diagnosed by FNA biopsy, the typical next step in management is a total thyroidectomy with or without a limited anterior neck lymph node dissection. If there were an imaging modality that could accurately stage the cancer prior to surgery, there might be a way to optimize the extent of surgery to maximize therapeutic benefit and minimize morbidity.

There is very limited literature examining the ability of FDG PET or PET/CT to stage thyroid cancer at the initial diagnosis. With respect to staging of the primary lesion ("T" staging), Jeong et al. recently examined the ability of PET SUV to predict extrathyroidal invasion of 1 cm or less papillary thyroid cancers. By multivariate analysis they found that age greater than 45 and ultrasound findings demonstrating the tumor adjacent to the external

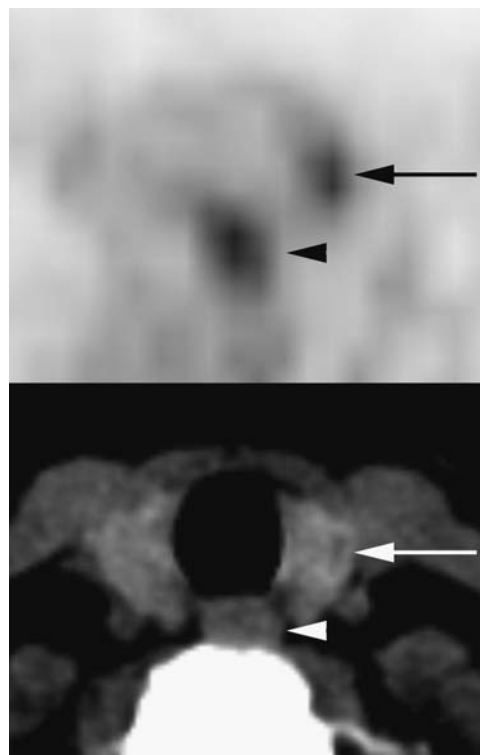


Figure 3 Incidental focal intense FDG uptake (SUV 8.1) (*black arrow*) within a hypodense thyroid nodule (*white arrow*) in a 48 year-old female undergoing PET/CT for breast cancer. FNA of a 6 mm hypoechoic nodule at this location on ultrasound revealed a colloid nodule. Note physiological esophageal activity (*arrowheads*). *Abbreviations:* SUV, standardized uptake value; FNA, fine needle aspiration.

thyroid capsule were predictive of extrathyroidal invasion. PET SUV was not predictive of the extent of tumor, and, therefore, they concluded that the need for more extensive surgery may be best selected by ultrasound and the age of the patient (31).

There is no literature examining the utility of FDG PET or PET/CT in the identification of lymph node or distant metastases ("N" and "M" staging) in individuals who are newly diagnosed with thyroid cancer. Since many patients with residual papillary and follicular thyroid cancer have iodine-avid disease at initial diagnosis, the mainstay of initial staging will remain with I-131 scintigraphy in the immediate postoperative setting while under thyroid hormone withdrawal or after recombinant thyroid stimulating hormone (TSH) stimulation. Identification of distant metastases may be limited to those patients with aggressive primary thyroid tumors (such as undifferentiated or anaplastic carcinoma) who are at higher risk for distant metastases (Fig. 4).

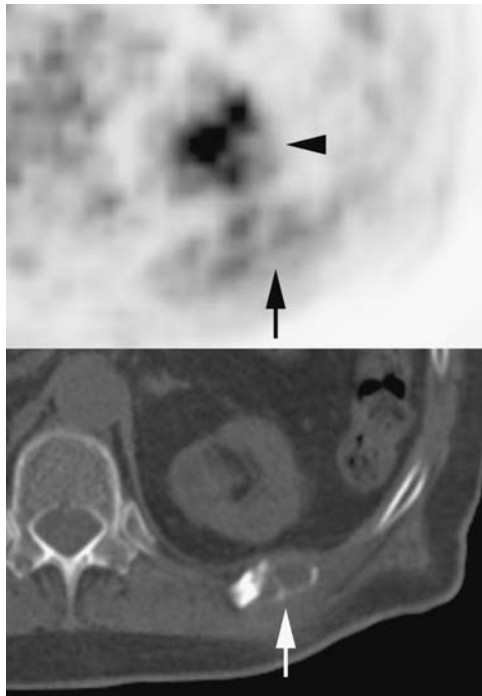


Figure 4 76 year old male with diffusely metastatic papillary thyroid carcinoma. An expansile lytic left rib metastasis (*white arrow*) demonstrates only moderately intense metabolic activity (*black arrow*). Note physiological urinary activity in the left kidney (*arrowhead*).

Recurrence Detection

There is considerable literature concerning the use of FDG PET or PET/CT in the detection of recurrent thyroid cancer. Standard protocols employing surgery and I-131 therapy have been very successful for managing most patients first diagnosed with thyroid cancer, and treatment challenges have been primarily in patients with recurrent disease. Prior to FDG PET and PET/CT, the primary means for restaging patients with suspected recurrent disease (in recent years identified through an elevation in serum thyroglobulin levels) was limited to repeat I-131 scintigraphy and ultrasonography of the neck. These methods remain useful to identify patients who benefit from repeat I-131 therapy for iodine-avid disease or further surgery for non iodine-avid resectable tumor.

There is, however, a significant subpopulation of patients with rising serum thyroglobulin levels who have both a negative I-131 scan and no bulky disease detectable by physical examination, neck ultrasound, or other imaging modalities (Fig. 5). Until the advent of FDG PET and PET/CT in this situation, further management was restricted to empiric I-131 therapy or, in select cases, an extensive cervical lymph node dissection.

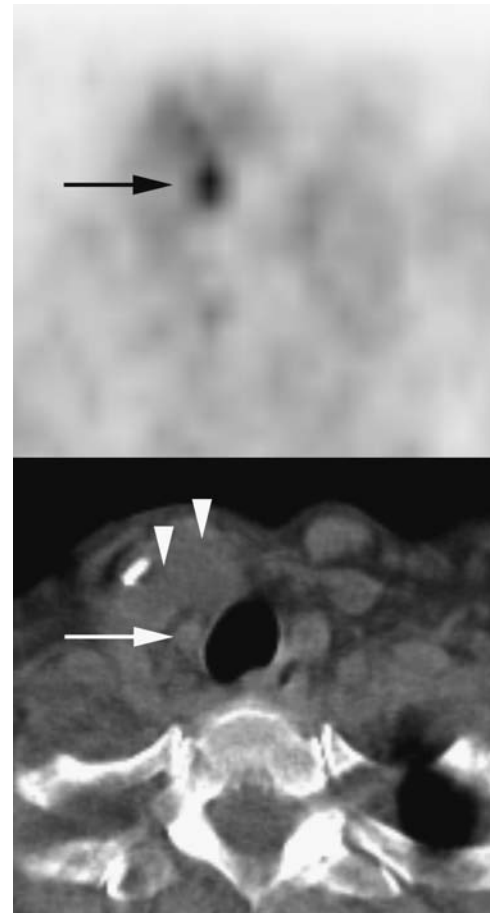


Figure 5 83-year-old female status post thyroidectomy and radioiodine therapy four years prior due to locally metastatic thyroid cancer. The patient presented with a negative I-131 scan, negative neck ultrasound and an unstimulated serum thyroglobulin level of 6 ng/mL. PET/CT revealed a 6-mm focus of locally recurrent disease in the right lower thyroid bed (*arrows*). The carotid artery and jugular vein are situated anteriorly (*arrowheads*).

In an attempt to look for new ways of localizing disease in this subpopulation of patients, researchers investigated the utility of FDG PET. Prior research suggested that recurrent iodine-negative disease tended to be aggressive and less differentiated, and investigators hypothesized that such tumors might be more metabolically active and thus more glucose-avid, therefore lending themselves to detection by FDG PET. This hypothesis was confirmed in early studies demonstrating that many metastases that were I-131 negative were FDG positive. I-131 positive tumors were often FDG negative, leading to what became popularly called the “flipflop phenomenon” (32,33). In 1999, Chung performed FDG PET on a cohort of 54 postsurgically athyrotic patients with thyroid cancer

Table 2 FDG PET in Patients With a History of Thyroid Cancer and Negative I-131 Scans

Author	N	PET sensitivity	PET specificity	Tg sensitivity
Feine, 1996	34	94%		All elevated ^b
Dietlein, 1997	11	63.4%		85.7%
Chung, 1999	54	94%	95%	54%
Wang, 1999	37	70%	76.5%	49%
Alnafisi, 2000	11	100%		All elevated ^b
Helal, 2001	38	70%		

^aIn patients with elevated Tg

^bElevated Tg was a criterion for entry

Abbreviation: Tg, thyroglobulin.

Source: From Refs. 7,34–36,39,40.

and negative I-131 whole body scans. Some patients had elevated thyroglobulin levels and others did not. They found a sensitivity of 93.9% for detection of metastases in 31 patients with proven disease compared with a sensitivity of thyroglobulin levels of only 54.5%. PET findings were negative in 20 of 21 patients ultimately determined to have no disease by overall clinical evaluation, yielding a specificity of 95.2%. The authors noted that in their patient population, PET was superior to I-131 imaging and thyroglobulin measurement for the detection of cervical nodal metastases (34).

Wang had slightly less optimistic results in a study of 37 patients with detectable thyroglobulin and negative I-131 scans. FDG PET identified the disease with a sensitivity of 71%. Management was reportedly altered in 19 of 37 patients on the basis of PET results (7). Alnafisi et al. also found a reasonable performance for FDG PET in patients with negative I-131 scans and elevated thyroglobulin levels. In their study, 11 patients were studied, and all had FDG uptake in the neck or mediastinum. Biopsy of PET-avid lesions yielded malignancy in six patients, was nondiagnostic in two, and had normal findings in 1. Two patients did not undergo biopsy because of normal ultrasound imaging. Management was changed in 7 of 11 patients by addition of PET (35).

Helal et al. examined patients with elevated thyroglobulin levels and negative I-131 scans following surgery and ablation for differentiated thyroid cancer. Patients were split into two groups, one containing detectable disease by conventional imaging, and one with no detectable disease. FDG PET identified 17 of 18 sites already identified by conventional imaging and detected 11 additional sites of the disease in these patients. PET also detected the disease in 19 of 27 patients with negative conventional imaging. Twenty-nine of 37 patients underwent a change in management, 14 of whom attained a disease-free status after additional surgery (36).

Several other papers have confirmed the utility of FDG PET in the setting of elevated thyroglobulin and negative

I-131 scintigraphy (37,38). In this setting with a negative physical exam and negative neck ultrasound, it is certainly the next test of best choice (Table 2).

In 2000, Moog et al. evaluated the accuracy of FDG PET for the detection of metastatic thyroid cancer while patients remained on thyroid hormone replacement therapy (TSH suppression) compared with detection during thyroid hormone withdrawal. Ten patients underwent FDG PET within 42 days while on and off thyroid hormone. Seventeen lesions were found on both studies, and the tumor-to-background ratio increased in 15 (3.85 vs. 5.84) patients when comparing TSH suppression with TSH stimulation. By carefully measuring absolute count rates, the authors found that the observed difference was due to both an increase in lesion uptake and a decrease in background activity, presumably because of the metabolic changes associated with hypothyroidism and elevated TSH (41). In a smaller study in 2002, van Tol et al. studied eight patients during TSH suppression and thyroid hormone withdrawal. New lesions were found in one patient with TSH withdrawal and four patients with positive findings during suppression had more intense uptake during withdrawal. Additional lesions were identified in two of the four patients under withdrawal. Clinical management was altered in two of eight patients (42). These preliminary findings echo the literature surrounding I-131 scintigraphy in patients with thyroid cancer and suggest that in order to maximize scan sensitivity, patients should undergo thyroid hormone withdrawal or thyrogen stimulation prior to imaging with FDG PET.

In 2002, Petrich examined the efficacy of FDG PET in thyroid cancer following the administration of exogenous recombinant human TSH (rhTSH), a method of TSH stimulation that is useful in patients who may not tolerate thyroid hormone withdrawal. Thirty patients with positive or equivocal thyroglobulin levels and negative I-131 scintigraphy underwent FDG PET while under TSH suppression and following TSH stimulation with rhTSH. The number of “tumor-like lesions” increased from 22 to

78 when comparing TSH suppression with rhTSH stimulation, and tumor-to-lesion ratios and SUV values also increased. They concluded that rhTSH stimulation is more sensitive than TSH suppression in patients undergoing FDG PET (43). Chin et al. also found similar findings in a small study of seven patients. Studies performed under rhTSH stimulation identified four additional lesions not seen during TSH suppression and one patient was positive on rhTSH stimulation alone (44). These findings suggest that for patients unable to undergo thyroid hormone withdrawal (including the elderly and individuals with morbidity during prior withdrawals), rhTSH stimulation may be an accurate and more sensitive alternative to imaging during suppression.

There is one study examining the utility of either thyroid hormone withdrawal or rhTSH stimulation in preparation for PET/CT in patients with thyroid cancer. In 2006, Saab et al. scanned 15 patients with elevated thyroglobulin levels and negative I-131 scans. Seven patients were prepared with thyroid hormone withdrawal, and 8 underwent rhTSH stimulated FDG PET/CT scans. Positive results were seen in four hypothyroid patients and five prepared with rhTSH. Positive findings were seen even in patients with relatively low stimulated thyroglobulin levels (13 and 14 $\mu\text{g/L}$). Six patients underwent surgery and 5 were identified with malignant tissue (45). This study suggests that rhTSH stimulation might be equally effective compared with hormone withdrawal, but is not of sufficient power or quality of design to draw definitive conclusions. There has not yet been a prospective comparison of the accuracy FDG PET or PET/CT during thyroid hormone withdrawal compared to rhTSH stimulation. Such a study would be technically challenging but not impossible.

In summary, preliminary data suggests that PET or PET/CT following thyroid hormone withdrawal or rhTSH stimulation is more accurate than PET or PET/CT performed during thyroid hormone suppression. Higher quality prospective trials would be helpful to compare rhTSH stimulation and hormone withdrawal and also to prove the superiority of these techniques compared with scanning the patient while on thyroid hormone.

PET and Treatment Response

FDG PET has emerged as a useful tool for assessing early response to therapy in a variety of malignancies, often before tumors change in size on anatomic imaging exams. Clinicians are now using FDG PET/CT to assess the effectiveness of therapy, and treatment modifications are common in patients with early progression of disease. While most of this work has been done in Hodgkin's disease, lung cancer, and other non-thyroidal neoplasms, a

few investigators have begun to examine the effectiveness of PET or PET/CT for assessing treatment response in thyroid cancer.

There are reports of novel situations in which PET has proven useful to assess treatment response in ways that compliment or replace the gold standard of I-131 imaging. In 2000, Robbins demonstrated in two patients with lung metastases of thyroid cancer that FDG PET could be useful in predicting the response to octreotide therapy (46). In 2001, Wang demonstrated that patients with positive FDG PET scans were more likely to progress (as measured by changes in serum thyroglobulin levels) following radioiodine therapy compared with patients with negative scans who typically responded to therapy (47). Application of this data to the general population of thyroid cancer patients with negative scans could significantly affect treatment decisions related to radioiodine therapy.

Blum and colleagues reported on the discovery of an incidental thyroid cancer in a patient with Hodgkin's disease. Follow-up PET after chemotherapy demonstrated a dramatic response to therapy with focal residual tissue at the base of the neck that was biopsied and shown to be thyroid cancer. This paper highlighted the concept that if all other lesions improve on PET and one any lesion persists, one must consider the possibility of a coexisting neoplasm that is not responding to the administered therapy (48).

Boerner et al. examined the utility of FDG PET to predict the response to isotretinoin therapy, an agent that is known to promote redifferentiation of more aggressive subtypes of thyroid cancer. Twenty-one patients with advanced thyroid cancer underwent I-131 and FDG PET imaging before and during therapy at 3-month intervals. The authors found that a decrease in FDG uptake at 3 months predicted an increased in I-131 uptake and tended to be associated with improved outcome. They propose that FDG PET might be useful in predicting which patients will benefit from prolonged isotretinoin therapy (49).

There has been no systematic evaluation of the use of FDG PET or PET/CT for treatment response measurement in more conventional situations such as patients with negative I-131 scans who are found to have focal or multifocal residual disease on PET. It would be intuitive to conclude that repeat imaging after additional surgery or radiation therapy might be useful in assessing response to therapy, but no formal studies demonstrate the utility of PET or PET/CT in this situation (Fig. 6). For now we are left with one case report by Larson in which a patient with a large, recurrent neck mass was followed by FDG PET which was predictive of the response to multiple doses of I-131 therapy and also octreotide therapy. (50) This measured response was not compared with CT, MRI, ultrasound, or any other imaging modality, and the most

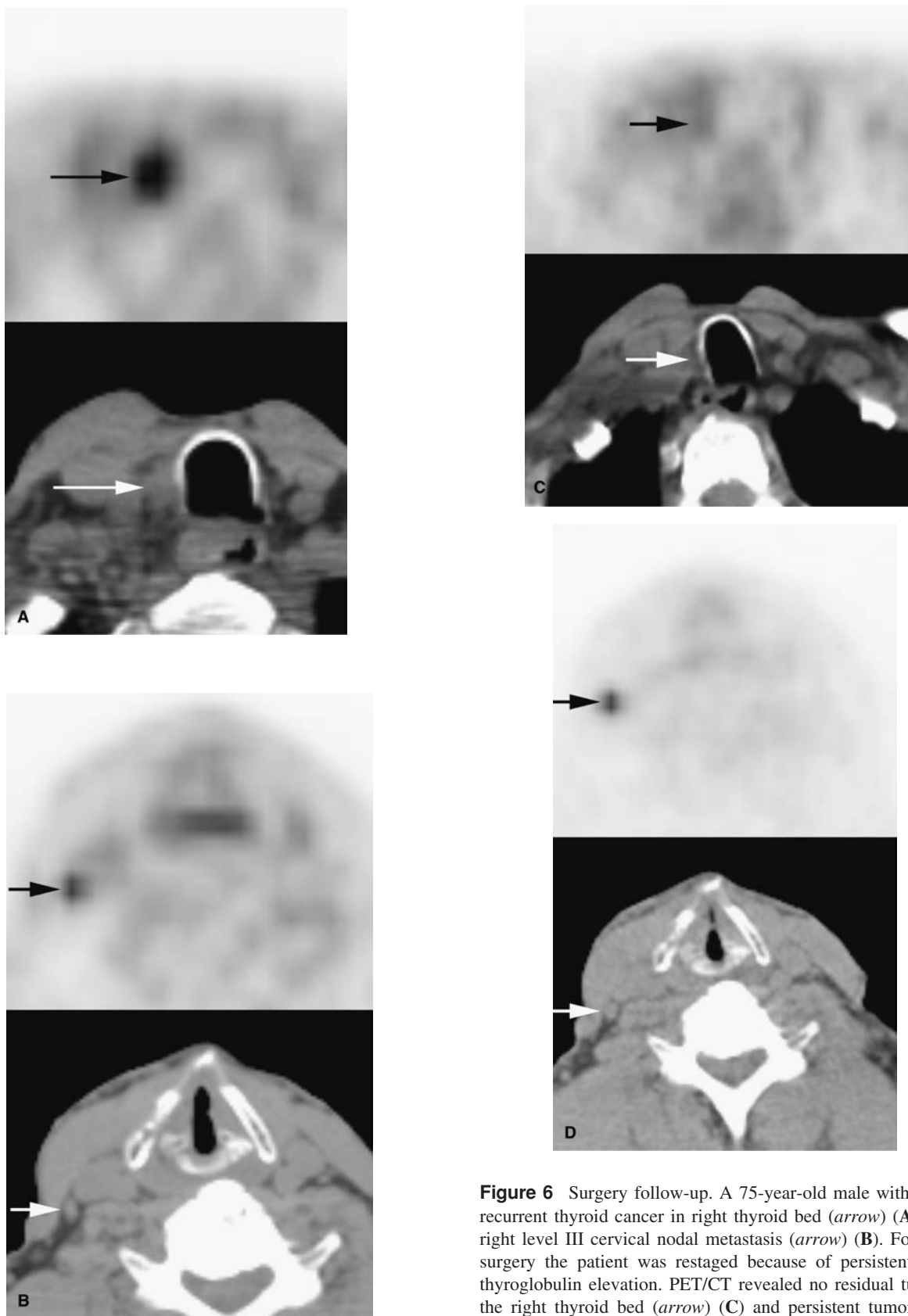


Figure 6 Surgery follow-up. A 75-year-old male with locally recurrent thyroid cancer in right thyroid bed (*arrow*) (A) and a right level III cervical nodal metastasis (*arrow*) (B). Following surgery the patient was restaged because of persistent serum thyroglobulin elevation. PET/CT revealed no residual tumor in the right thyroid bed (*arrow*) (C) and persistent tumor in the subcentimeter right neck node (*arrow*) (D). PET/CT identified persistent tumor that was not apparent by any other modality.

effective use of PET/CT in these situations remains undefined.

PET and Prognosis

In addition to its service as a tool for detecting recurrent disease and assessing treatment response, FDG PET has been investigated as a prognostic tool in thyroid cancer. In 2000, Wang and colleagues retrospectively examined 125 patients with recurrent thyroid cancer who were restaged with FDG PET. While univariate analysis demonstrated reduced survival in individuals with age greater than 45 years, distant metastases, PET positivity, high FDG uptake and high volume of FDG-avid disease, multivariate analysis demonstrated that the volume of FDG-avid disease was the single strongest predictor of survival (51).

Robbins et al. looked at a larger sample of 400 patients and found that age, initial stage, histology, thyroglobulin, radioiodine uptake, and PET findings correlated with survival through univariate analysis. Through multivariate analysis, only age and findings at PET were found to be predictors of survival. They found that a negative PET scan in a patient with recurrent disease conferred a favorable survival advantage compared to a positive FDG PET result, and suggested that aggressiveness of therapy should be linked to the findings on PET (52).

Schonberger and colleagues have elucidated the biological link between prognosis and glucose uptake as measured by FDG PET. In their 2002 study, these investigators examined the expression of glucose transporters (types 1–5) in formalin-fixed and paraffin-embedded tissue specimens from 45 patients with varying types of thyroid cancer (53). They found increased levels of glucose transporter type 1 (GLUT1) expression in neoplasms with unfavorable prognoses including anaplastic thyroid cancer (ATC) and biologically more aggressive follicular cancers. Low or no GLUT1 expression was measurable in patients with normal thyroid tissue or well-differentiated tumors. These findings demonstrate that GLUT1 is associated with more aggressive thyroid cancers and likely explains the mechanism for increased glucose avidity on FDG PET.

THYROID INCIDENTALOMAS ON PET

Focal thyroid uptake on FDG PET is encountered in 1.2% to 4.3% of all patients undergoing evaluation for other malignancies (11,54–59) and can be because of benign adenomas, nodular hyperplasia, focal thyroiditis, Hashimoto's thyroiditis (Fig.7), thyroid cancer, metastatic disease, or lymphoma (60). Focal uptake has also been reported in thyroglossal duct cysts (61).

Numerous investigators have retrospectively examined the incidence of malignancy within incidentally discovered

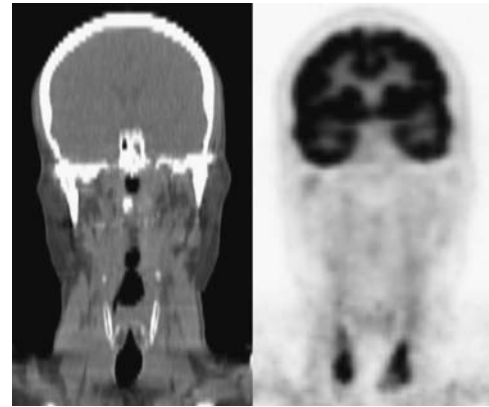


Figure 7 A 60-year-old male with lymphoma and hypothyroidism. PET/CT demonstrates intense FDG uptake throughout the thyroid due to Hashimoto's thyroiditis.

focal thyroid lesions on PET or PET/CT. The papers with large patient populations (excluding Yi et al.) demonstrate that of the biopsied focal thyroid incidentalomas on PET, 14–50% are malignant. This range could potentially be overestimated because of the fact that not all foci of FDG uptake are biopsied, and lesions associated with a more worrisome constellation of clinical or imaging features (and a consequently increased the risk of malignancy compared with all lesions) might be more likely to be biopsied and thus bias the results. Nevertheless, this data does suggest that the incidence of malignancy is high enough to warrant further investigation with ultrasound and/or FNA biopsy. Despite statistically significant differences in SUVmax reported in several studies, some authors demonstrate either a lack of significance [Kim et al. (58)] or a large overlap [Choi et al. (62)] in SUVmax between benign and malignant lesions (6.7 ± 5.5 vs. 10.7 ± 7.8 , respectively) (Fig. 4). The author of this text does not recommend relying on SUV to differentiate between benign and malignant lesions; not only because of this reported data, but also because the known variation in SUV between small and large lesions, effects of body habitus, blood glucose level, and partial volume averaging.

In 2006, Choi incorporated the CT appearance of thyroid incidentalomas into a diagnostic algorithm for evaluation of focal thyroid uptake found on PET/CT. Seventy of 1,763 (4.0%) patients had focal FDG uptake and 49 lesions were confirmed as malignant or benign by biopsy or follow-up (36.7% of all focal thyroid uptake was malignant). Receiver-operator characteristic analysis generated an area under the curve (AUC) of 0.701 when using SUV as the only diagnostic criteria. The AUC significantly improved to 0.878 when FDG-avid lesions demonstrated low density on CT, nonvisualization on CT, or were accompanied by diffusely increased uptake in the remainder of the thyroid. Although maximum SUV was

significantly higher in malignant lesions (10.7 vs. 6.7), the range for malignant (2.2–32.9) versus benign (2.3–33.1) lesions was similar and underscores the difficulty in relying on SUV alone for diagnosis (11). It remains to be seen whether or not the CT findings in this study can be confirmed by other investigators. In contrast to Choi, Yi et al. reported on a series of 6 incidental thyroid lesions on PET in which all 4 malignant lesions were low-attenuation on CT (59). Until additional studies are completed, the reader should exercise great caution when considering incorporating the CT findings into scan interpretation.

In conclusion, any focal accumulation of FDG in the thyroid has a moderate risk of malignancy and, if not already characterized, should be further evaluated by ultrasonography. Any nodules identified in the region of FDG uptake should be biopsied, and CT appearance or CT density should not affect management unless more research clarifies its potential value.

ADVANTAGES OF PET/CT OVER PET

When considering the complex nature of anatomical structures and their relationships in the neck, a single PET/CT examination that generates both metabolic and anatomical data in a precisely coregistered format is at first examination quite compelling. In thyroid cancer, there is emerging literature examining the incremental benefit of PET/CT compared with PET alone. In a 2003 case report, Chin and Patel initially reported on the potential ability of PET/CT to precisely differentiate between normal vocal cord activity and adjacent tumor (63). In that same year, Bockisch and colleagues in a brief paper suggested PET/CT was more useful than PET alone for localization of MTC (64). Finally in 2003, Zimmer et al. performed PET/CT on 8 patients with elevated serum thyroglobulin levels and negative radioiodine scans. Four patients had positive scans and all 3 individuals undergoing surgery had pathological confirmation of recurrence for 6 of 8 lesions identified on PET/CT (65). A weakness of this study is that it did not compare PET/CT with other modalities.

In 2005, Nahas et al. reported on a retrospective study of 33 patients with recurrent papillary thyroid cancer that PET/CT localized the disease in 22 of 33 patients for a per-patient sensitivity of 66%. Twenty patients underwent surgery and PET/CT was correlated with histopathological findings in 25 of 36 sites yielding a per-lesion accuracy of 70%. PET/CT was 100% specific for identifying recurrent disease on a per-patient basis. The authors state that PET/CT was most useful when serum thyroglobulin levels were greater than 10 ng/mL and when tumors did not concentrate radioactive iodine (66).

In 2006, Palmedo published a direct comparison of PET alone, CT alone, side-by-side PET and CT, and finally integrated PET/CT. Forty patients with iodine-

negative recurrent disease underwent PET/CT. Separate reading sessions revealed a sensitivity of 79% for PET alone and CT alone and a sensitivity of 95% for side-by-side and integrated PET/CT. A clear advantage for PET/CT was revealed by a specificity of 91% compared with 76% for PET, 71% for CT and 76% for side-by-side CT. The increased specificity (and overall accuracy of 93% compared with 75–85% for other modalities) for PET/CT was attributed primarily to a reduction in false positive findings in the neck where physiological activity had been confused with tumor (Fig. 7). Overall, PET/CT led to a change in therapy in 48% of patients (67).

Finally in 2006, Zoller et al. retrospectively evaluated 47 PET/CT scans performed on 33 patients with differentiated thyroid cancer, elevated thyroglobulin levels and negative I-131 scans. PET and CT scans were interpreted independently and then compared with a consensus PET/CT reading session performed by a nuclear medicine physician and radiologist reading together. PET/CT was reported as positive in 74% of all scans, altered the diagnosis compared with PET alone in 77%, and altered treatment in 23% of all examinations (68). This study is limited in that PET/CT was considered a gold standard compared with CT and PET and there was no pathological or follow-up proof of the findings. It does however demonstrate that PET/CT alters scan interpretation and provides sufficient evidence to stimulate prospective trials that may more definitively measure the potential benefits of PET/CT.

In summary, PET/CT does appear superior to PET alone, and when available should be employed in the restaging of patients with elevated thyroglobulin, negative I-131 scans and no evidence of cervical lymphadenopathy by physical exam or ultrasound.

Hurthle Cell Thyroid Carcinoma

Hurthle cell thyroid carcinoma (HTC) is a rare form of differentiated thyroid cancer that comprises oxyphilic follicular cells that produces thyroglobulin, but in only some cases concentrate radioiodine. Prognosis is worse compared with papillary and follicular cancer, likely because of decreased responsiveness to I-131 therapy and more biologically aggressive behavior (69).

There is scant literature examining the efficacy of FDG PET in the evaluation of HTC. In 1996, Blount demonstrated the ability of FDG to detect HTC (70). In 2002, Plotkin et al. combined their own data with prior series and generated a meta-analysis revealing a sensitivity of 92%, a specificity of 80%, a positive predictive value of 92%, a negative predictive value of 80% and an accuracy of 89% for FDG PET in the detection of recurrent HTC (69).

Lowe et al. retrospectively evaluated the efficacy of FDG PET in one patient undergoing initial staging and

11 patients undergoing restaging of HTC. They found intense FDG uptake in all but one of the known lesions, and PET identified disease in 7 of 14 scans at locations not identified by other modalities. PET identified more extensive disease compared with other modalities in 7 of a total of 14 scans. They reported that the additional information provided by PET guided or altered therapy in these patients (71).

In 2006, Pryma et al. retrospectively reviewed 44 patients with HTC who underwent FDG PET and conventional imaging with CT, ultrasound, and radioiodine scintigraphy. They found a sensitivity of 95.8% and a specificity of 95% for FDG PET that was superior to CT and radioiodine scintigraphy. They also reported that SUVmax was greater than 10 within lesions predicted a reduced 5-year survival (72).

In summary, it is clear that FDG PET is the imaging test of choice for restaging patients with HTC. Little is known about its utility in initial staging and thus, further study is needed. Advantages of PET/CT over PET may be inferred, but are yet to be proven.

Insular and ATC

Insular thyroid carcinoma is a rare subtype of thyroid cancer that has not been systematically studied with PET. Zettinig et al. report a case of false-negative lung metastasis that was iodine-avid, further documenting the “flip-flop phenomenon” of thyroid cancers that are either FDG-avid or I-131-avid, but often not both (73).

ATC is a rare and aggressive, poorly differentiated, noniodine-avid form of thyroid cancer with aggressive clinical behavior and poor 1-year survival. Scant literature exists regarding the utility of PET in this subgroup of patients. Poppe reported a case of ATC with lung metastases that was FDG-avid on PET (74). A few other reports of FDG-avid ATC were reviewed by Khan and colleagues (75). The exact role of FDG PET or PET/CT in ATC, if any, is yet to be determined.

MTC

MTC is a neuroendocrine tumor consisting of thyroid parafollicular C-cells (Fig. 8). Surgery is the mainstay of initial treatment and this tumor is not iodine-avid. Treatment of local recurrence and metastases is primarily surgical and, therefore, accurate localization of disease is essential. FDG PET has been evaluated in the detection of MTC, most frequently in patients previously treated surgically, but those of whom subsequently present with elevated serum calcitonin and/or carcinoembryonic antigen levels (Fig. 9).

Gasparoni et al. first reported on the potential utility of FDG PET for MTC in 1997. They found in 3 preoper-

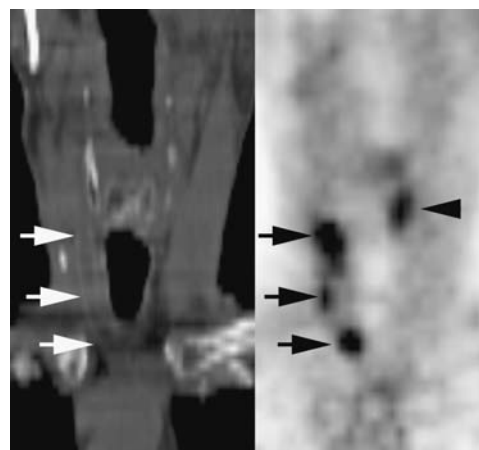


Figure 8 False positive. A 52-year-old male status post thyroidectomy due to papillary thyroid cancer three years prior. PET/CT was performed because of elevated serum thyroglobulin and negative I-131 scan. Images demonstrate multifocal intense uptake (*black arrows*) fusing with the right carotid artery on CT (*white arrows*), which was later found to be occluded by platelet thrombus. Note also incidental asymmetric left vocal cord activity (*arrowhead*).

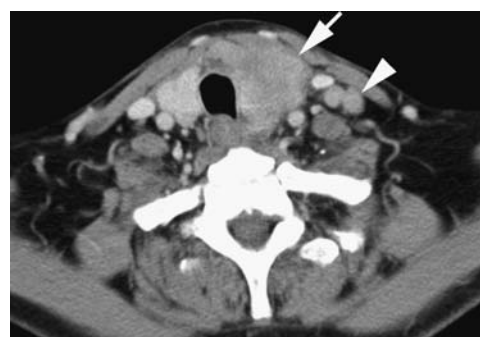


Figure 9 A 57-year-old female with newly diagnosed locally invasive medullary thyroid carcinoma. Contrast-enhanced CT demonstrates a heterogeneously enhancing left thyroid mass with ill-defined borders (*arrow*). Moderately enhancing adjacent cervical nodal metastases are seen (*arrowhead*).

atively staged patients, FDG PET performed similarly to conventional imaging modalities for detecting the primary tumor and local metastases (Fig. 10). PET was the only technique that detected a lung metastasis. In one of two patients undergoing restaging, FDG PET was the only modality to find mediastinal relapse (76). Similarly, Musholt reported in that same year that FDG PET detected 31 foci of the disease in 10 patients with suspected recurrent disease (Fig. 11) compared with

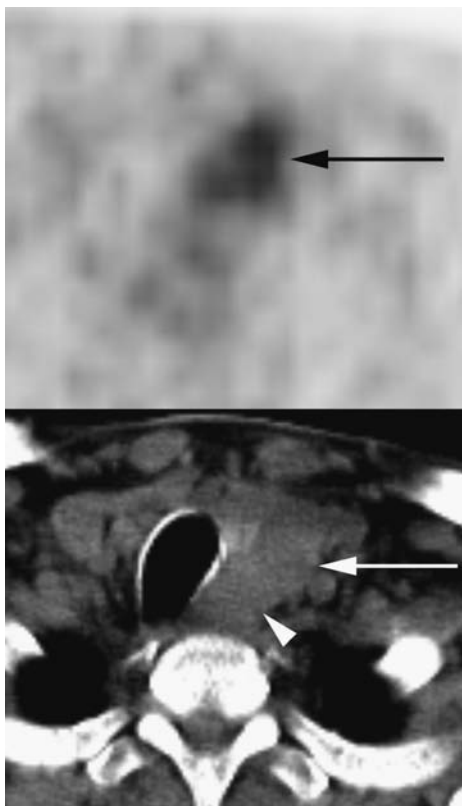


Figure 10 A 56-year-old male with biopsy proven medullary thyroid carcinoma proven to be locally invasive at surgery. PET/CT demonstrates a metabolically active mass in the left thyroid (arrows) with an ill-defined border between the mass and esophagus posteriorly on CT (arrowhead).

11 foci by CT and MRI (77). Brandt-Mainz et al., in 2000, demonstrated a sensitivity of 76% for the detection of recurrent disease among 20 patients with rising calcitonin levels following initial surgery (78).

In 1998, Adams compared the efficacy of FDG PET with a combination of ^{99m}Tc -DMSA and ^{111}In -pentetreotide scintigraphy in a variety of neuroendocrine tumors. In patients with MTC and rapidly rising tumor markers, the traditional scintigraphic techniques detected 3 lesions in 2 patients, whereas FDG PET detected 1 pulmonary, 3 bone, 20 mediastinal, 10 locoregional, and 4 liver metastases in 7 patients (79). Similarly, Diehl compared FDG PET with ^{111}In -pentetreotide, ^{99m}Tc -DMSA and ^{99m}Tc -sestamibi scintigraphy and CT and MRI in 82 patients following thyroidectomy, and 3 patients prior to surgery for MTC. They found a sensitivity of 78% and a specificity of 79% for FDG PET compared with a sensitivity of 25% to 33% and specificity of 78% to 100% for scintigraphic techniques and 50% and 20% for CT. MRI yielded a similar sensitivity of 82% but sensitivity was slightly reduced compared with FDG PET at 67% (80). Szakall has also

reported a higher sensitivity for FDG PET compared with other modalities for detecting recurrent MTC (81,82). A recent study by de Groot noted a sensitivity of 96% for FDG PET that was superior to octreotide, DMSA, CT, MRI, ultrasound, and bone imaging (83). Gotthardt reported similar performance of CT and FDG PET that was superior to somatostatin receptor scintigraphy, concluding that the combined CT and PET might be the most appropriate study for restaging MTC (84).

There is little data evaluating the possible incremental benefit of combined PET/CT compared with single or combinations of other imaging modalities. Bockisch reported in 2003 that PET/CT offered an advantage over PET or CT alone in 3 of 12 patients by more precisely localizing abnormal tissue and improving the feasibility of directed surgery (64).

Alternatives to FDG have not yet found routine clinical use but remain promising as PET imaging continues to grow. Gourgiotis reported in 2003 a case of metastatic MTC of the parapharyngeal space detected by ^{18}F -fluorodopamine, a norepinephrine transporter substrate (85). In 2001, Hoegerle and colleagues compared the diagnostic accuracy among fluorinated dihydroxyphenylalanine (^{18}F -DOPA), FDG-PET, somatostatin receptor scintigraphy and conventional imaging (CT/MRI) for the evaluation of patients with MTC who presented with elevated calcitonin levels. All functional techniques had a sensitivity of 66% for detection of primary tumors or local recurrence. F-DOPA was more sensitive (88%) for local lymph node metastases compared with FDG-PET (44%) and somatostatin receptor scintigraphy (50%). All functional modalities were approximately 90% specific for all tumor types. Conventional imaging demonstrated higher sensitivity for primary tumors and local recurrence (100%), and was moderately sensitive for the detection of local lymph node metastases (69%). Specificity was limited at 55% to 57%. Conventional imaging was also more sensitive for distant metastases but lacked specificity and the authors conclude the F-DOPA can be a useful supplement to other imaging techniques (86). It remains to be seen if alternative tracers will improve upon the performance of FDG.

In conclusion, FDG PET is occasionally equal in performance and often superior compared with CT, MRI, and traditional scintigraphic imaging techniques in the evaluation of patients with suspected recurrent MTC. FDG PET/CT is probably the imaging test of choice for restaging patients with either rising calcitonin or CEA levels following surgery.

PET In Hyperthyroidism

PET has been used to study glucose metabolism in patients with Graves' disease. In 1998, Boerner and colleagues performed PET on 36 patients with this

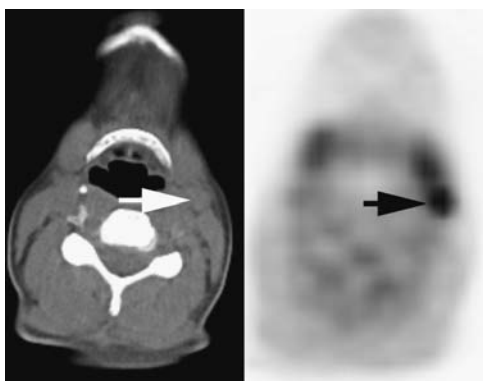


Figure 11 A 57-year-old female with a history of medullary thyroid carcinoma, status post thyroidectomy four months prior. PET/CT reveals a 5-mm left cervical nodal metastasis (arrow) that by CT criteria would have been considered benign.

condition and found enhanced glucose uptake in the thyroid because of both increased fractional blood volume and greater cellular utilization of FDG. FDG uptake correlated positively with increasing antithyroid antibody levels and shorter radioiodine half-life, but it was unclear if these metabolic changes were due to lymphocytic infiltration or alterations in thyroid epithelial cell physiology (87).

PET has been useful in the study of metabolic changes outside of the thyroid. Bengel et al. performed ^{11}C -acetate cardiac PET on 10 patients with mild hyperthyroidism. Follow-up imaging in euthyroid patients following treatment was also performed. Prior to therapy, heart rate and cardiac output were increased, and peripheral vascular resistance was reduced. Oxidative metabolism in the heart as measured by ^{11}C -acetate PET was higher during hyperthyroidism, but overall cardiac efficiency as measured by a “work metabolic index” (WMI), was unchanged between hyperthyroid and euthyroid states. Their conclusion was that hyperthyroidism does not effect the overall performance characteristics of the myocardium (88).

PET In Hypothyroidism

PET has been used to study the effects of hypothyroidism in patients under thyroid hormone withdrawal following thyroidectomy. Bengel and colleagues studied 10 patients using ^{11}C -acetate cardiac PET following surgery for thyroid cancer. Images were acquired during thyroid withdrawal and again following adequate replacement of thyroid hormone. During the hypothyroid state, systemic vascular resistance and left ventricular mass were higher, and ejection fraction and stroke work index were lower. These changes were associated with a decrease in myo-

cardial efficiency as measured by a WMI. The authors concluded that since cardiac work decreased more than rates of oxidative metabolism, the overall efficiency of the myocardium is reduced in hypothyroidism (89).

PET has also been used to examine the brain in patients with hypothyroidism. In 2001, Constant et al. used quantitative ^{15}O - H_2O and ^{18}F -FDG PET to show that hypothyroid patients with symptoms of depression, anxiety, and psychomotor slowing exhibit a generalized reduction in both cerebral perfusion and glucose metabolism. This metabolic change is in contrast to euthyroid patients with primary depression who typically demonstrate regional changes in blood flow and glucose metabolism (90).

BEYOND FDG: OTHER TRACERS

Investigators have taken advantage of the quantitative capabilities of PET for purposes of radioiodine dosimetry. Eschmann et al., in 2002, performed PET of the thyroid using ^{124}I -sodium iodide and demonstrated that accurate estimates of radiation dose could be obtained for patients undergoing treatment of thyroid cancer or hyperfunctioning thyroid nodules (91). In 2004, Sgouros demonstrated that 3D volumetric analysis of ^{124}I -sodium iodide PET could be used to accurately predict I-131 dose in patients with multiple iodine avid thyroid cancer metastases (92).

^{124}I -sodium iodide also shows promise as a potential diagnostic imaging agent. Freudenberg compared ^{131}I -sodium iodide whole body scintigraphy with ^{124}I -sodium iodide PET, CT, and combined ^{124}I -sodium iodide PET/CT and found a sensitivity of 56%, 87%, and 100% for PET, CT, and PET/CT, respectively, compared with 83% for whole body scintigraphy (93). These promising early results require confirmation and this technique may become useful if or when ^{124}I -sodium iodide becomes more available in the United States.

CONCLUSIONS

FDG PET and PET/CT now play a vital role in the management of patients with thyroid cancer. Although limited as a modality for diagnosis and initial staging, it is the imaging test of choice in patients with I-131 scan-negative recurrent disease. Performance of PET/CT in this situation is probably best while the patient is under TSH stimulation. PET and PET/CT have an emerging role in Hurthle cell, insular, anaplastic, and MTCs. As a research tool, PET has been useful in the study of metabolic changes associated with hyperthyroidism and hypothyroidism, and new tracers demonstrate promise for imaging patients with thyroid cancer. Finally, incidental focal thyroid uptake at PET or PET/CT requires further clinical evaluation.

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PET/CT: Mediastinal Lesions

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INTRODUCTION

The mediastinum is the central area of the thorax that contains the major visceral organs and structures of the thorax other than the lungs. The heart, aorta and great vessels, and the trachea are the major structures. Computed tomography (CT) has a major role in the characterization of mediastinal lesions. While ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) imaging provides contributory information for diagnosis, its major role is reserved for staging and the follow-up of malignant mediastinal tumors. Discussion will emphasize both the CT and FDG PET characteristics of mediastinal lesions in addition to PET's role in the management, and follow-up of these lesions.

MEDIASTINAL ANATOMY: MEDIASTINAL COMPARTMENTS

The division of the mediastinum into visual compartments on the lateral radiograph has been performed to assist in developing a differential diagnosis for lesions. While abnormalities may occur in multiple regions, some lesions have a predilection for a specific area.

In the Felson classification system (Table 1), the anterior mediastinum includes the heart (Fig. 1) (1). The posterior aspect of the heart and the anterior aspect of

the trachea represent the boundary of the anterior compartment. The middle region runs to a longitudinal line 1 cm posterior to the anterior aspect of the vertebral bodies, and the posterior mediastinum occupies the remainder of the mediastinum, ending at the anterior aspect of the ribs.

There are three divisions in the Fraser and Paré classification (Fig. 1) (1). The anterior mediastinal compartment in this system runs from the posterior aspect of the sternum to the anterior aspect of the heart and aorta. The middle mediastinum begins at the posterior aspect of the anterior division, and runs to the posterior aspect of the heart and trachea. The posterior mediastinum runs to the anterior aspect of the posterior ribs.

DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL LESIONS WITH CONSIDERATION OF LOCATION

For clarity, the Felson classification system will be used in this chapter for establishing a differential diagnosis for lesions. Certain lesions have a propensity to originate in particular compartments of the mediastinum (Table 2). Anterior mediastinal lesions are most commonly related to lymphoma, Hodgkin's disease most often, thymoma, teratoma, and thyroid enlargement or masses. Hodgkin's disease frequently involves the anterior mediastinum, in up to 85% of cases at presentation (2). Middle mediastinal lesions are

Table 1 Mediastinal Compartments in the Felson and Fraser and Paré Classification Systems and Contents

Compartment	Contents Felson	Contents Fraser and Paré
Anterior	Heart, ascending aorta, thymus, fat, nodes, brachiocephalic veins	Thymus, fat, nodes, brachiocephalic veins
Middle	Aortic arch, trachea, paratracheal nodes, esophagus, descending thoracic aorta	Heart, ascending aorta and aortic arch, trachea
Posterior	Paravertebral fat, spine, nerves	Esophagus, descending thoracic aorta, paravertebral fat, spine, nerves

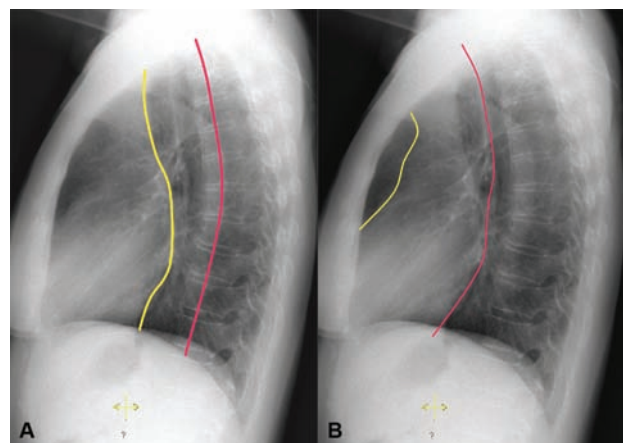


Figure 1 Divisions of the mediastinum according to (A) the Felson (A) and Fraser and Paré (B) classification systems on lateral chest radiograph: In the Felson classification system (A), the anterior compartment runs to the anterior aspect of the trachea and posterior aspect of the heart (yellow line). The middle compartment runs to a longitudinal line drawn 1 cm posterior to the vertebral bodies (red line). Posterior compartment is posterior to the middle mediastinum, extending to the back of the thorax. In the Fraser and Paré division of the mediastinum (B), the anterior compartment lies anterior to the ascending aorta and heart (yellow line). The middle mediastinum runs to the back of the trachea and heart (red line). Posterior compartment is behind the middle compartment.

typically nodal or vascular. Esophageal and airway pathology are also considerations, including the bronchogenic cyst. Posterior mediastinal abnormalities are typically related to the spine, nodes, nerves, and fat in the paraspinal region. Infection, hematoma, and vascular processes always remain considerations despite mediastinal location.

While separation of the mediastinum into compartments is a useful method to begin the development of a differential diagnosis, such an approach cannot be applied dogmatically. For example, lesions in the mediastinum may originate in one compartment and spread to the adjacent compartment (Fig. 2) and the mediastinal compartment as defined on CT may project on lateral radiograph over another compartmental area (Fig. 3).

Table 2 Typical Locations for Specific Mediastinal Lesions

Compartment	Mediastinal lesions
Anterior	Thymic lesions (thymoma, thymic hyperplasia, thymic carcinoid, thymolipoma) Germ cell neoplasm (teratoma and other histologies) Lymphoma Thyroid enlargement (goiter, mass) Cardiophrenic angle masses (Morgagni hernia) Cardiac and pericardial masses (pericardial cyst)
Middle	Ascending aortic aneurysm Lymphadenopathy, lymphoma Bronchogenic cyst Esophageal masses (leiomyoma, duplication cyst, carcinoma) Tracheal masses (primary and metastatic) Descending aorta and aortic arch aneurysms Mediastinal venous collaterals
Posterior	Neurogenic lesions (nerve sheath, sympathetic chain, paraganglia) Lymphadenopathy Spinal lesions (infection, fracture with hematoma, tumor, dural ectasia, neuroenteric cysts) Extramedullary hematopoiesis Thoracic splenosis Diaphragm (congenital Bochdalek hernia, traumatic rupture)

PET studies have demonstrated a higher degree of FDG uptake in malignant mediastinal tumors than in benign entities (Table 3) (3). PET imaging may be non-specific, with an overlap of activity between benign and malignant entities. In this context, CT is helpful for morphologic characterization to improve the diagnosis of specific mediastinal pathology since specific CT characteristics may aid in narrowing the differential diagnosis (Table 4). The attenuation of a lesion is helpful, as cystic lesions with thin walls are likely to represent congenital

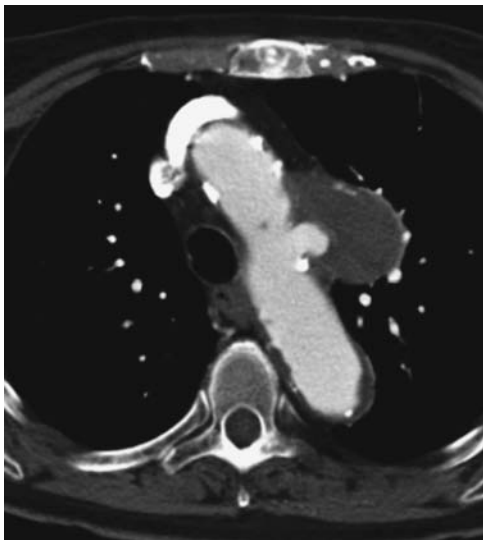


Figure 2 Penetrating aortic ulcer involving middle and posterior mediastinal compartment. On contrast enhanced axial CT section, a large penetrating aortic ulcer appears as a rounded contrast opacified structure extending outside the lumen, however, contained within the wall of the distal aortic arch. Soft tissue surrounding is consistent with associated intramural hematoma and overall aneurysmal dilatation of the aorta. The process involves the middle and posterior compartments.

cysts such as bronchogenic, esophageal, neuroenteric, thymic, and pericardial cysts (Table 5). Lymphangiomas are multiloculated fluid-containing lesions that can occur in the superior mediastinum typically from direct extension from the neck and axilla. These lesions envelop and insinuate among the mediastinal structures. Fluid can occur in soft tissue masses, and in this scenario, malignancy would be the primary consideration. Low-attenuation lesions may also be schwannomas or neurofibromas reflecting lipid content (4) and soft tissue. Fluid attenuation may also be present in tumors representing necrosis, so PET activity and thick walls would increase suspicion for this possibility. Calcification is identified in treated lymphoma, teratomas, vascular etiologies, occasionally thymomas, sympathetic ganglia tumors, and calcifying metastases.

For the anterior mediastinal lesions, which have appearances similar to one another, CT characteristics may prove especially useful. In the presence of an anterior mediastinal mass, additional nodes in the vicinity or the appearance that the mass comprises a confluence of nodes are suggestive of lymphoma over a thymic or germ cell neoplasm (Fig. 3). A thymoma is suggested when a soft tissue density solitary mass is identified with locally aggressive features. Thyroid tissue within the mediastinum has most commonly contiguity with the thyroid gland. High attenuation is noted on precontrast images

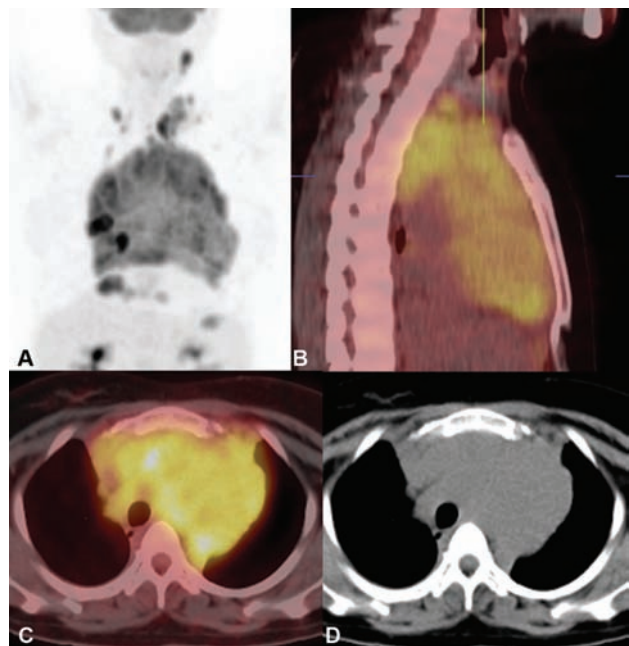


Figure 3 Anterior mediastinal lymphoma: A 23-year-old man with newly diagnosed Hodgkin's disease. The anterior view from a maximum intensity projection of the FDG PET (A) study shows an extremely extensive area of uptake in the mediastinum in addition to other areas of adenopathy. The sagittal view from the fused PET/CT (B) shows that the mass is in the anterior mediastinum. The transaxial fused PET/CT (C) and the CT scan (D) from that study show a homogeneous mass on the low dose CT scan with heterogeneous activity. It is the additional adenopathy that narrows the differential diagnosis toward lymphoma.

secondary to iodine content, and intense and frequently heterogeneous enhancement occurs after contrast administration. Fat, fluid, and calcification are highly suggestive of a teratoma (Table 4).

In the ensuing sections, the morphologic characteristics of mediastinal lesions will be described that aid in distinguishing abnormalities with similar FDG uptake in addition to describing pertinent PET literature and findings for specific entities.

Table 3 PET Uptake of Mediastinal Lesions

Uptake	Mediastinal lesions
Increased	Malignant tumors, invasive thymoma, lymphoma, sarcoidosis
Intermediate	Myeloma, noninvasive thymomas, schwannoma
Low	Teratoma, benign cysts

Source: From Ref. 3.

Table 4 CT Characteristics that are Helpful for Differentiating the More Common Causes of Anterior Mediastinal Masses

Mass	Helpful CT findings
Lymphoma, more commonly Hodgkin's disease	Confluence of nodes
Thymoma	Solitary soft tissue mass, well circumscribed or locally invasive features with occasionally "drop metastases"
Teratoma	Solitary mass with combinations of fat, fluid, and calcification
Thyroid	High attenuation on pre- and postcontrast CT

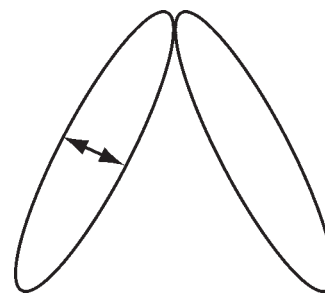
CHARACTERISTIC MEDIASTINAL PATHOLOGY

Thymus

Normal Thymus

An understanding of the normal appearance of the thymus is the key to recognizing the presence of pathology. The thymus is a glandular structure in the anterior mediastinum, anterior to the ascending aorta and pulmonary outflow tract, comprising thymocytes, epithelial cells, and mesenchymal cells (5). It has a variable appearance, depending upon the age of an individual. It occupies the largest amount of the thorax in neonates and early infancy; however, the thymus achieves its maximum size at adolescence, after which involution occurs when it decreases in size and weight. Histologically, the normal thymus in this age group shows a dual cell population, both epithelial cells and lymphocytes, including immature T cells. Additionally there are perivascular spaces and medullary differentiation (6). The gland will be encapsulated.

The thymic gland morphology on imaging is most typically of a bilobed structure of equal limb size with communication in the most anterior and superior aspect of the gland (5,7–9). The lobes do not connect in 36% of cases (7). The thickness (Fig. 4) of the thymic gland limbs are typically on average $1.1 \text{ cm} \pm \text{SD } 0.4 \text{ cm}$ when 6 to

**Figure 4** Measurement of thymic limb thickness. Thymic thickness (*double-headed arrow*) is measured perpendicular to the long axis of the thymic lobe.

19 years of age and $0.8 \text{ cm} \pm \text{SD } 0.2 \text{ cm}$ when 20 to 29 years of age (8). In children, the thymic contours typically are mildly convex on the lateral aspects with undulating margins. Normal thymic activity is commonly seen on PET in children and even up to young adulthood (10,11). Uptake in normal, unstimulated thymus has been reported even into the fifth decade (12). On FDG PET, the thymus activity takes on the usual inverted "Y" configuration best appreciated in the coronal plane. On PET/CT, this will conform to the morphologically normal thymic tissue.

The thymus after adolescence is gradually replaced by fat. The lateral margins of the thymus become straight or concave, assuming a more triangular appearance. The limb thickness gradually decreases, and the thymus undergoes near-complete fatty involution usually by 40 years of age, although residual thymic tissue is evident in up to 74% at this age (7). Persistent thymus was identified in 17% of individuals past 50 years of age (7). When present, a more linear appearance of the soft tissue density has been described (8). The remaining soft tissue density may also maintain a triangular (7) or oval (8) configuration. Persistent thymus in individuals aged 50 years or older has limb thickness typically on average less than $0.5 \text{ cm} \pm \text{SD } 0.15 \text{ cm}$ (7). Rarely is only one limb visualized; and therefore, if present, pathology should be suspected (7) (Fig. 5). Some findings suggest that the uptake of FDG is inversely related to the density on CT (13).

Table 5 Cystic Mediastinal Lesions

Entity	Attenuation	Location
Bronchogenic cyst	Ranges from simple fluid to high attenuation (milk of calcium and proteinaceous contents)	Subcarinal, right paratracheal, occasionally intrapulmonary
Pericardial cyst	Simple fluid	Anterior cardiophrenic angle
Esophageal duplication	Fluid attenuation	Distal esophageal wall
Neuroenteric cyst	Fluid attenuation	Associated with hemivertebra in spinal region
Meningocele	Fluid attenuation	Costovertebral junction
Thymic cyst	Simple fluid, may be hemorrhagic or proteinaceous	Thymic region in the anterior mediastinum

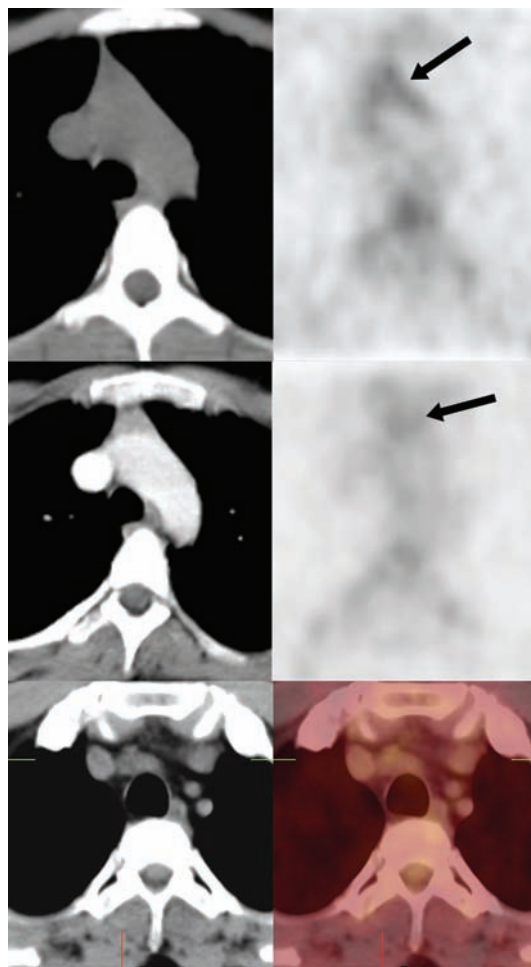


Figure 5 Normal thymus. (*Top row*) CT and FDG PET slice in a 14 year old with a newly diagnosed GIST tumor. Note the inverted “Y” configuration of the FDG accumulation (*arrow*) and the relatively prominent soft tissue. (*Middle row*) Contrast CT and FDG PET in the same patient at age 18 years. The only treatment had been surgery two years earlier. Here the size of thymus is slightly less, the shape has changed, and the activity (*arrow*) has decreased. (*Bottom row*) A 43-year-old man with a solitary pulmonary nodule and a small amount of residual thymic tissue, but without any evidence of activity on the fused FDG PET/CT image.

Thymic Hyperplasia

Thymic hyperplasia is enlargement of the thymus while maintaining its normal gross architecture and histology. Enlargement typically occurs after cessation of chemotherapy or steroids, and findings have been reported on both CT and PET. This so-called rebound phenomenon is characterized by the infiltration of plasma cells and the presence of lymphoid follicles in the thymus, which occurs in the recovery phase after steroid- or

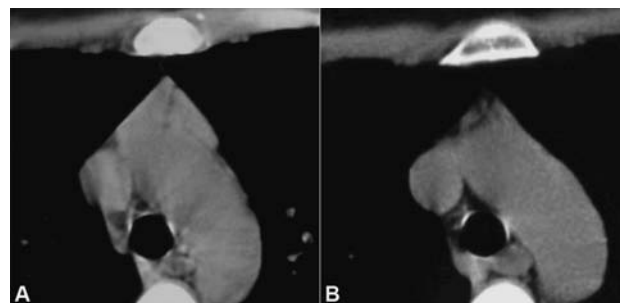


Figure 6 Thymic hyperplasia in a 42-year-old female with Graves’ disease. Axial CT (**A**) demonstrates that the thymic gland is larger than expected for a patient of this age. Preservation of the normal bi-lobed structure with central median region is present. After therapy for thyroid disease, the patient’s thymus on CT (**B**) approaches an appearance that is expected for the patient’s age.

chemotherapy-induced apoptosis and inhibition of lymphocyte proliferation (14). Thymic hyperplasia has also been reported after radioiodine therapy for thyroid cancer (15,16). Thyroid disease, particularly Graves’ disease, has also been associated with thymic hyperplasia (Fig. 6) (17,18). On CT, thymic hyperplasia is most noticeable when the thymic size enlarges in comparison with a baseline CT. Otherwise identification of hyperplasia may be difficult, particularly given the age-dependent variable appearance of the thymus. Thymic hyperplasia on CT appears as an enlarged thymic gland maintaining its bilobed structure. The lobes may have convex borders.

On FDG PET, thymic hyperplasia is characterized by mild-to-moderate uptake in a normally shaped gland. Standardized uptake values (SUVs) reported have averaged between 1.8 and 3.8 (12,14). An SUV less than 4 is compatible with thymic hyperplasia; above that intensity, other entities should also be considered (13). Since the thymic gland reaches its maximal size at adolescence and then gradually undergoes fatty involution, thymic hyperplasia is most noticeable in individuals over 40 years of age since only minimal soft tissue component and little metabolic activity should normally be present. While thymic hyperplasia is touted to be more common in children and adolescents, occurring in 75% of this age group after chemotherapy (14), it can be seen regularly in young adults and even in middle-aged to elderly patients (16) (Fig. 7). It can persist for well over a year after the cessation of therapy.

To differentiate thymic hyperplasia from a mass, hyperplasia is suggested when there is a bilobed structure that is centered at midline, as opposed to a solitary mass or multiple masses that are located on either side of midline. Heterogeneity and calcification are not typically identified in hyperplasia. While the limbs of the thymic gland in hyperplasia can have convex borders, the gland does not

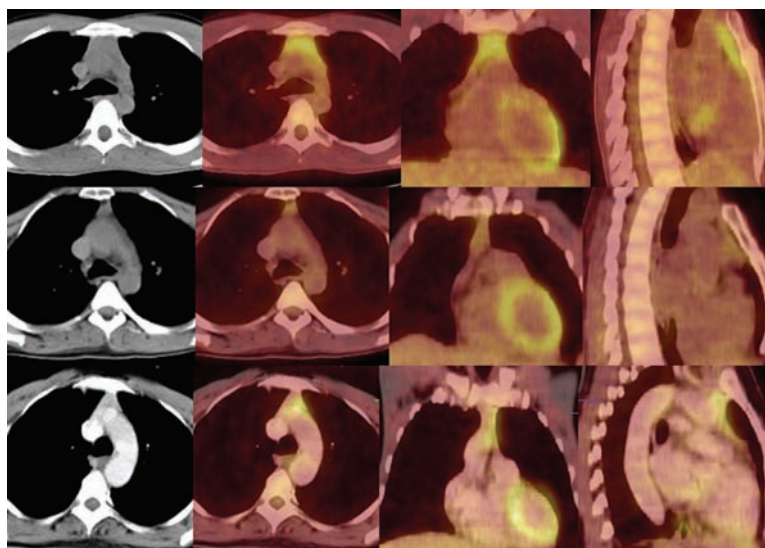


Figure 7 Three different patients with thymic rebound following chemotherapy. CT, transaxial, coronal, and sagittal fused PET/CT (*top row*) in a 21-year-old one year after a complete response to chemotherapy for NHL. The active thymus has the typical inverted “Y” configuration on the coronal image. The thymic tissue appears normal on CT given the patient’s age but had increased from a prior study thereby indicative of thymic rebound. CT, transaxial, coronal, and sagittal fused PET/CT (*middle row*) from a 42-year-old woman three months after adjuvant chemotherapy for breast cancer. The thymic soft tissue is slightly prominent for a patient this age yet maintains the expected shape of the thymus consistent with rebound. (*Bottom row*) A 62-year-old woman treated with chemotherapy for breast cancer. The thymic soft tissue is large for a patient of this age. The three examples illustrate the range of FDG uptake that can occur with thymic rebound.

typically appear round (Table 6). In general, heterogeneity of FDG uptake supports the diagnosis of a thymoma (19), and as intensity increases, neoplasm becomes more likely.

In myasthenia gravis, patients exhibit a form of hyperplasia termed lymphoid follicular hyperplasia (LFH). The follicles in the thymus in this scenario are hyperplastic, and the overall thymus may be enlarged or normal in size. Therefore, the demonstration of an enlarged thymus in an individual with myasthenia gravis is suggestive of LFH; however, the absence of macroscopic enlargement does not imply that LFH is not present. FDG PET uptake has been reported in patients with thymic hyperplasia associated with myasthenia gravis (19). In a normal-appearing

thymus on CT, FDG uptake might be suggestive of involvement.

Thymoma/Invasive Thymoma/ Thymic Carcinoma

Thymoma is a neoplasm of thymic epithelial origin. Thymomas have been clinically associated with myasthenia gravis in 15% of the cases, with approximately 45% of patients with thymomas having myasthenia gravis. Thymic hyperplasia of the lymphoid follicular nature has been associated with myasthenia gravis more frequently, with up to 75% of patients with myasthenia gravis having thymic hyperplasia. A number of paraneoplastic syndromes have been associated with thymoma, such as hypogammaglobulinemia, pure red cell aplasia, and Lambert-Eaton myasthenic syndrome (20).

Pathologically, the classification of thymomas has been in evolution. Classification systems by Bernatz, Lattes and Jonas, Levine and Rosai, Marino and Müller-Hermelink and subsequent variations, and Verley and Hollmann have been used in the past. More recently, a unified classification system proposed by the World Health Organization was issued in 1999 (6) (Table 7). Thymic neoplasms were divided into types A, B, and C. The subgroup B comprised B1, B2, and B3 constituents according to the increase of proportion and atypia of thymic epithelial tissue in relation

Table 6 Thymic Hyperplasia Vs. Mass

Thymic hyperplasia	Thymic mass
Homogeneous attenuation	Heterogeneity, calcifications
Bilobed structure with limbs greater than expected for age	Unilateral soft tissue mass with discrete nodular areas possibly within
Triangular configuration centered at midline	Solitary or multiple round/oval lesions
SUV < 4–5 ^a	SUV > 4–5 ^a

^aThere is significant overlap in SUV values between hyperplasia and thymomas.

Table 7 Histologic Classification of Thymic Neoplasms

Suster and Moran	WHO	Histologic features
Well-differentiated thymoma	Type A	Spindle- or oval-shaped neoplastic epithelial cells and nuclei
Well-differentiated thymoma	Type AB	Round and spindle or oval epithelial cells and nuclei
Well-differentiated thymoma	Type B1	Round epithelioid cells, lymphocyte rich
Well-differentiated thymoma	Type B2	Scattered large epithelial cells, vesicular nuclei, distinct nucleoli, prevalent lymphocytes
Atypical thymoma	Type B3	Predominantly round or epithelial polygonal cells, no or little atypia, few lymphocytes
Thymic carcinoma	Type C	Cytologic atypia with features more in common with other epithelial neoplasias

Source: From Refs. 6.

to lymphocytes within the thymus. B3 constituents would correlate with the term well-differentiated carcinoma that is used with the Müller-Hermelink classification. Type C included those tumors with a high degree of atypia that were no longer specific to the thymus but rather similar to carcinomas identified in other organs. The varying types of thymoma were felt to represent increasing degrees of malignancy as type C was approached. Basically, types A, AB, and B1 are considered low-risk thymomas and B2 and B3 higher-risk thymomas (21). A variation proposed by Suster and Moran entails use of poorly, moderately, and well-differentiated terminology to described tumors along the spectrum of thymoma, such as thymoma, atypical thymoma, and thymic carcinoma (6). The role of histologic classification in predicting the behavior of thymoma is at best controversial. It does seem clear that these classifications contribute to prognostication, although staging at the time of diagnosis and the ability to resect these tumors are equally important (6).

Regardless of the pathological classification, thymic neoplasms range from less to more aggressive on imaging. Typical well-encapsulated noninvasive thymoma or the more indolent forms of thymoma appear as solitary, well-circumscribed soft tissue masses in the thymic region, whose cranial aspect lies near the thoracic inlet and its caudal location at the diaphragmatic level (Fig. 8). As opposed to thymic hyperplasia, thymomas are unilateral. Calcification and cystic areas can occur in up to 31% and 40% cases, respectively, with greater propensity for aggressive lesions (22).

The term invasive thymoma has been used when invasion of the tumor capsule is identified upon pathology (Fig. 9). The presence of direct invasion on imaging is suggested when there is stranding in the fat surrounding the mass, loss of the fat planes with the adjacent mediastinal organs and lungs, and encasement of vessels. The identification of pleural metastases is indicative of invasive behavior. PET/CT may delineate lymph node and pleural involvement as well (21). CT and magnetic resonance imaging (MRI), however, have a limited role in assessing for invasion of apparently well-circumscribed

thymomas. Jeong et al., in a review of 91 cases of thymic epithelial tumors that underwent resection, demonstrated that CT had a limited role in differentiating histological subtypes. However, it was helpful in predicting those associated with worse prognosis. Lobulated or irregular tumors, mediastinal fat or great vessel invasion, and pleural seeding, not surprisingly, were associated with a higher recurrence and metastatic rate (22). Mediastinal fat invasion is more common in thymic carcinoma and invasive thymomas than noninvasive thymoma, and irregular contours are significantly more often associated with thymic carcinoma than low-grade thymoma (21). Nonetheless, tumor necrosis, calcification, marked enhancement, great vessel invasion, or pericardial effusions, pleural seeding, and lymph node enlargement may occur across the spectrum of thymic neoplasm (21). Thymic carcinoma can mimic the appearance of thymoma on imaging (Fig. 10). However, thymic carcinoma can spread to lymph nodes and have distant metastases. Thymoma, on the other hand, is usually more locally invasive, although distant metastases have been reported even in

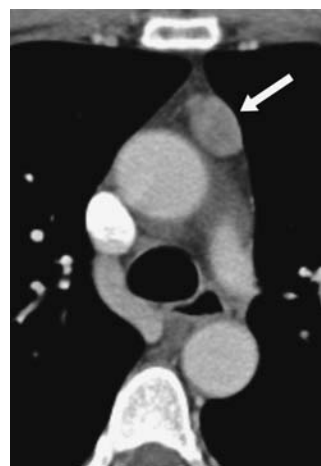


Figure 8 Noninvasive thymoma. Soft tissue density on axial contrast CT is well circumscribed and corresponds to a thymoma (arrow) in a patient with myasthenia gravis.

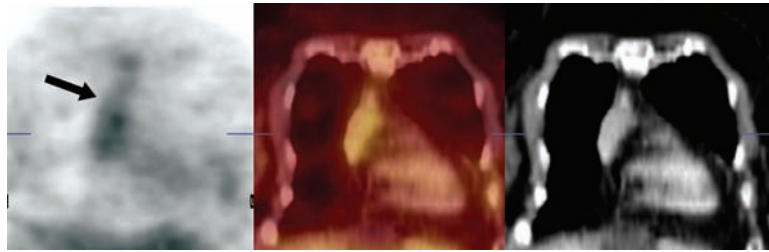


Figure 9 Invasive thymoma. A 73-year-old woman with a history of lymph node-negative, intermediate thickness melanoma. This anterior mediastinal mass was incidentally noted on PET/CT. Coronal FDG PET (A) and fused (B) images demonstrate slightly heterogeneous uptake (*arrow*) with a maximum SUV of 3.7. CT coronal image from the PET/CT demonstrates a rather smooth contour belying the capsular invasion seen at pathology consistent with an invasive thymoma.

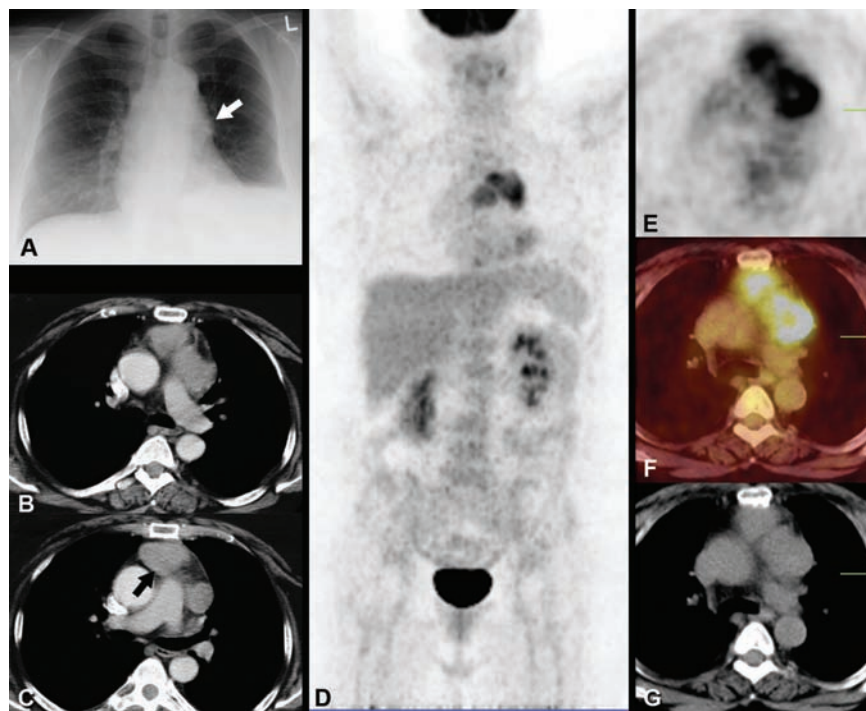


Figure 10 Thymic carcinoma in a 58-year-old female. Chest radiograph (A) demonstrates a lobulated contour to the left mediastinum (*arrow*). CT scan with contrast (B,C) demonstrates a lobulated mass with mild calcifications (*arrow*). Anterior MIP from the FDG PET/CT (D) scan demonstrates increased uptake with high metabolic activity and an SUV of 7.7. By CT appearance, this thymic carcinoma cannot be differentiated from a thymoma. However, both the PET intensity (E) and the heterogeneity suggest a more aggressive tumor. Corresponding fused (F) and noncontrast CT (G) slices from the PET/CT are shown.

type B1 (21). Staging is typically performed according to the Masaoka clinical-pathologic system.

PET imaging of thymic neoplasms was studied by Sasaki et al., who described a mean SUV of 7.2 ± 2.9 for thymic carcinoma ($n = 9$), 3.8 ± 1.3 for invasive thymoma, and 3 ± 1 for noninvasive thymoma (Figs. 9 and 10). The authors achieved reasonable sensitivity (84.6%), specificity (92.3%), and accuracy (88.5%) for differentiating thymic carcinoma from thymoma, when

using an SUV of 5 as a cutoff (23). No statistically significant difference in SUV between invasive and non-invasive thymomas was identified, consistent with the similarity of the two tumors. Liu et al. also failed to demonstrate a significant difference in the FDG uptake between different stages of thymoma (19). However, heterogeneity of uptake supports a diagnosis of invasive thymoma over noninvasive (19) (Figs. 9 and 10). Brink et al. presented one case of thymic carcinoma with an SUV

of 9.6 (14). More recently, Sung et al. demonstrated a significant difference in SUV between thymic carcinomas and thymomas, but not between noninvasive and invasive thymomas. In this series, the average maximum SUV for noninvasive thymoma was 4.0 ± 0.42 , for invasive thymoma 5.6 ± 1.9 , and for thymic carcinoma 10.5 ± 4 (21). On the basis of these limited data, it appears that high FDG PET associated with morphologic features of a thymic neoplasm raises the possibility that a lesion is a thymic carcinoma.

The differentiation of invasive thymoma, noninvasive thymoma, and thymic hyperplasia by PET intensity may be more difficult, but inclusion of the pattern of uptake and CT characteristics may help. Furthermore, FDG PET (or PET/CT) may be helpful in staging of invasive thymomas and thymic carcinoma (19,21). In one series of 33 patients, lymph node metastases were identified on integrated PET/CT in 44%, some in normal-sized lymph nodes. Distant metastases to bone and liver were also identified. Interestingly, although FDG uptake was seen in pleural seeding, CT, either diagnostic or performed at the time of PET/CT, was more helpful in identifying pleural spread (21).

Other Thymic Abnormalities of Interest

The thymolipoma is a lesion that occurs in the thymic region, yet has a characteristic appearance. An entity described in young adults, this lesion primarily comprises fatty tissue with residual thymic tissue. The lesions can be large and, given their lipomatous component, conform to the mediastinal contours (Fig. 11). PET imaging has a limited role in the diagnosis of this lesion, given its characteristic appearance, but will show decreased metabolic activity.



Figure 11 Thymolipoma in an asymptomatic patient. (A) Axial CT demonstrates a mass comprised predominantly of fat attenuation interspersed with minimal residual thymic tissue. (B) sagittal MPR demonstrates the mass's large size and relative lack of mass effect.

Another thymic mediastinal lesion to consider in an individual with Cushing's syndrome is thymic carcinoid. The thymic carcinoid is difficult to differentiate by imaging from other thymic and anterior mediastinal neoplasms, appearing as a solitary soft tissue mass, but FDG uptake has been reported on PET. Interestingly, FDG PET had played a role in identifying recurrent/residual disease (24).

Thymic cysts are uncommon mediastinal cysts, either congenital, i.e., related to a patent thymopharyngeal duct, or acquired, i.e., related to an inflammatory process such as in HIV patients, in whom HIV infection can lead to thymitis. Cysts also may occur after treatment of lymphoma, prior thoracotomy, or in association with thymic tumors (25–28). Congenital thymic cysts have low attenuation of fluid and are well circumscribed with a thin wall. Inflammatory thymic cysts can be large-sized and more complex with loculations (26,27). Contents may be complicated fluid or gelatinous material, and the walls may be thick and fibrous. Typically, significant inflammation and fibrosis is present on histopathologic examination (26). A thymic cyst when infected or hemorrhagic can, however, be difficult to differentiate from cystic areas in a neoplasm and may, therefore, need to be resected to differentiate when there are soft tissue areas (26). PET imaging of thymic cysts has been reported to show relatively decreased uptake with an average SUV of 0.9 ± 0.1 (23) (Fig. 12). However, the presence of inflammation might change this.

Germ Cell Neoplasm (Teratoma)

Extragonadal germ cell neoplasms comprise approximately 10% of all germ cell neoplasms, with the mediastinum the most common extragonadal site (29,30). These germ cell neoplasms are felt to arise from multipotential primitive germ cells that are misplaced, typically occurring in the midline region. The diagnosis of a primary mediastinal germ cell neoplasm is made by exclusion of a primary in the testes and ovaries. Teratomas and seminomas are the most common histologies. Nonseminomatous germ cell tumors such as an endodermal germ cell (yolk sac), embryonal cell, choriocarcinoma, and mixed histologies comprise the remaining mediastinal germ cell neoplasms (31). Typically, clinical symptoms such as shortness of breath are associated with malignant forms of germ cell neoplasm. A paraneoplastic syndrome of limbic encephalitis has been reported with mediastinal germ cell tumors (GCTs), and increased FDG uptake in the brain consistent with an inflammatory lesion has been described (32,33).

Teratomas are the most common histology of germ cell neoplasms in the mediastinum. They are derived from typically greater than one germ cell layer. Mature teratomas are benign and most common, comprising 60% to

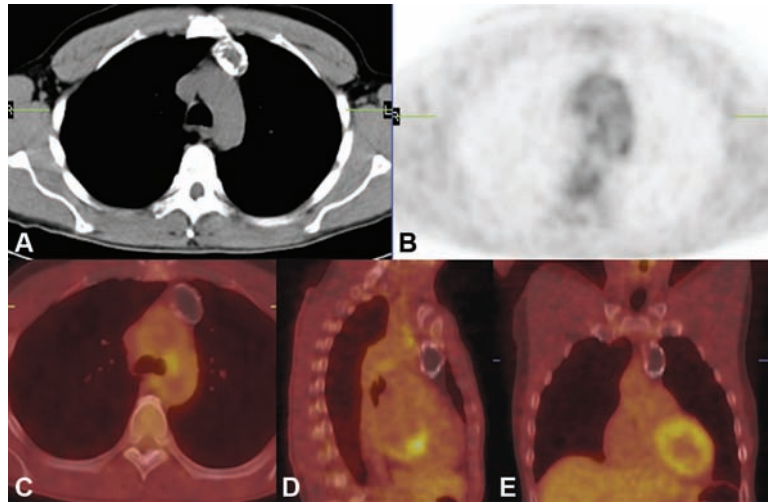


Figure 12 This 47-year-old man had a PET/CT after a screening CT scan showed a pulmonary nodule. The transaxial CT from the PET/CT (A) shows an irregularly calcified rim about the thymic cyst. The corresponding FDG PET (B) slice shows almost no activity associated with this. The transaxial (C), sagittal (D), and coronal (E) fused images simply show the characteristic anterior mediastinal location.

70% of mediastinal GCTs, followed by seminomas (31). There are immature forms containing fetal tissue in addition to malignant teratomas containing sarcomatous and carcinomatous histology. Teratomas most commonly occur in the anterior mediastinum, occurring in the posterior mediastinum approximately 3% to 8% of the time (34).

Teratomas classically demonstrate characteristic differentiated fat, lipid containing or simple fluid, and calcifications (Fig. 13). In a series reported by Moeller et al., of

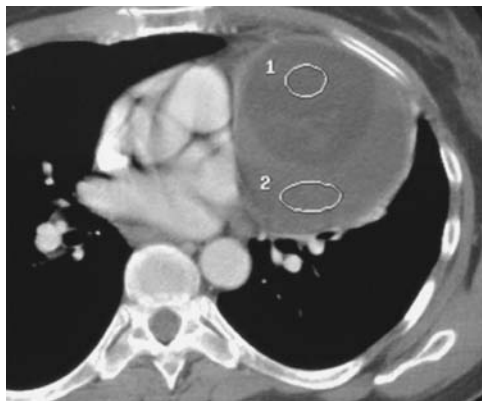


Figure 13 Teratoma in the anterior mediastinum. Axial CT scan with intravenous contrast shows a large mediastinal mass arising anterior to the heart suggests the lesion originates in the anterior mediastinum. On a lateral radiograph, such a mass may appear in the middle compartment also. Note the varying attenuations contained within the mass. A more anterior central area is consistent with liquid fat (-7.8 HU) while higher attenuation fluid components are present more posteriorly and peripherally. These findings are indicative of a teratoma.

66 mature teratomas, all had soft tissue attenuation, 88% had fluid, 76% had fat, and 53% had calcifications. The combination of soft tissue, fluid, fat, and calcium were noted in 39%. Soft tissue, fluid, and fat together were present in 24% with soft tissue and fluid present concurrently in 15%. Fat-fluid levels were present in 11% (35). Teratomas can rupture into the airways, pleura, and pericardium (36).

In a small series of teratomas, FDG PET identified three out of four malignant teratomas and correctly characterized six teratomas as mature. Importantly, FDG PET uptake after treatment will accurately identify recurrent disease and characterize response to therapy (37). In a more extensive series, including 12 mediastinal tumors, FDG PET had a 91% positive predictive value for post-treatment recurrence or residual disease but only a 62% negative predictive value (38).

The germ cell neoplasms other than teratoma are difficult to differentiate from other anterior mediastinal masses, given their soft tissue appearance. The presence of elevated α -fetoprotein or β -human chorionic gonadotropin levels should raise the question of an embryonal cell neoplasm (30,39).

Secondary germ cell neoplasms can spread to the mediastinum and neck, typically after other intra-abdominal lymphadenopathy is present (40). Paraesophageal and subcarinal metastases in a study by Wood et al. were demonstrated as the most commonly involved regions (40). Identification of metabolically active abnormality on PET should direct the use of additional therapy. The absence of PET activity carries a good prognosis in patients treated for metastatic germ cell neoplasms (37).

Vascular Lesions

Vascular abnormalities comprise a major category of mediastinal pathology. Vascular pathology, when present, can have significant clinical impact and may be misdiagnosed or overlooked, particularly on noncontrast CT. Identifying such pathology may be crucial, and consideration of this category of lesions is helpful to avoid overlooking these entities. Brief attention will be given to major vascular pathology in the mediastinum that can be identified on noncontrast CT, as an in-depth discussion of these entities are beyond the scope of this book.

The thoracic aorta comprises the sinus region, or the area of aorta below the sinotubular junction and above the aortic valve and annulus. The ascending thoracic aorta extends to the junction with the brachiocephalic artery, after which the aortic arch continues until the ligamentum arteriosum, with the portion between the left subclavian artery and the ligamentum arteriosum termed the isthmus. The descending thoracic aorta begins at the ligamentum and extends to the aortic hiatus in the diaphragm. The thoracic aorta caliber is most prominent in the ascending aorta tapering gradually as the more distal portions are approached. The caliber of the aorta increases with age. On average, in a study by Aronberg et al., the proximal ascending aorta had a caliber of 3.62 cm, distal ascending aorta 3.51 cm, proximal descending aorta 2.63 cm, mid-descending aorta 2.48 cm, and distal descending aorta 2.42 cm (41).

Aneurysms can arise from any vessel, typically arterial, most commonly the thoracic aorta. An aortic diameter greater than 1.5 to 2 times the normal caliber is traditionally considered aneurysmal. For practical purposes, dilatation greater than 5 cm in the ascending aorta can be considered aneurysmal while in the descending thoracic aorta greater than 4 cm can be utilized. Diffuse dilatation or ectasia can occur in which the entire aorta is symmetrically dilated.

Aneurysms are focal dilatations that may be fusiform or saccular in nature. Typically, fusiform areas of dilatation are elongated while saccular dilatation is focal and rounded. True aneurysms are dilatations comprising three layers of the aortic wall, which are the intima, media, and adventitia (42). While true aneurysms are either fusiform or saccular in shape, false or pseudoaneurysms that contain less than three layers of the aortic wall are typically saccular. Pseudoaneurysms have a higher likelihood of rupture.

On CT imaging, aneurysms can appear heterogeneous in nature, as they may contain varying attenuation related to thrombus within, as opposed to intraluminal blood. Calcifications are frequently identified in the aortic wall. Aneurysms may occur related to the heart and coronary bypass grafts.

Pathology involving part of the aortic wall can occur, such as aortic dissection, intramural hematoma, and penetrating aortic ulcer. On CT, intimal calcifications that are displaced centrally into the lumen are suggestive of blood, within the media of the aortic wall, either thrombosed hematoma or flowing blood. In this scenario, full assessment with contrast CT or MRI can be considered, particularly if suspected to involve the ascending aorta. On postcontrast CT imaging, differentiation of hematoma and flowing blood can be made. Intravenous contrast in the media of the aorta is termed a dissection, which begins typically when there is an intimal disruption that allows flowing blood and contrast to enter and dissect within the media longitudinally along the course of the aorta (Fig. 14). Involvement of the ascending aorta proximal to the left subclavian artery is considered a type A dissection, whereas distal to the left subclavian artery, the dissection is classified as a type B according to the Stanford classification. A type A dissection is considered a surgical emergency. Intramural hematoma without a definite etiology, when extensive, may represent a thrombosed dissection.

A focal area of intravenous contrast in the wall of the aorta can occur consistent with a penetrating ulcer that is typically formed when a plaque in the intima of the aorta ulcerates and ruptures into the media. A penetrating ulcer is considered and managed as a focal dissection (Fig. 2). On contrast CT, a focal typically rounded area of contrast that extends beyond the luminal confines into the aortic wall is noted and associated with intramural hematoma.



Figure 14 Type B dissection. MPR in the left anterior oblique plane obtained from a contrast enhanced MDCT shows a thoracic aortic Type B dissection beginning distal to the subclavian artery. Intimal disruption is identified.

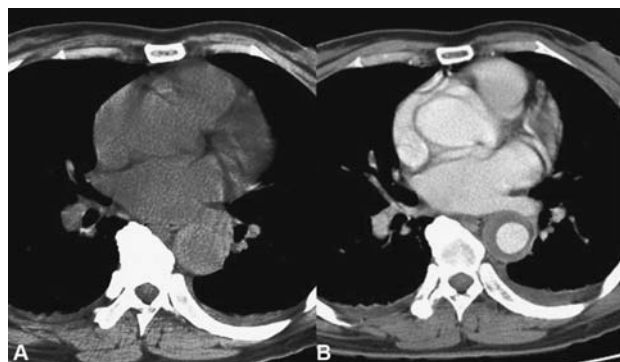


Figure 15 Intramural hematoma involving the descending thoracic aorta. Non-contrast CT (A) demonstrates a high attenuation in the descending aortic wall consistent with acute hemorrhage. After contrast administration, hematoma (B) in comparison with the intraluminal contrast appears low in attenuation, and the acute nature is not as evident.

Intramural hematoma can result from a penetrating ulcer, thrombosed dissection of the lumen, or unassociated with a demonstrable intimal disruption. On noncontrast imaging, crescentic high attenuation lining the periphery of the aorta should raise suspicion for an intramural hematoma that is acute, given high attenuation (Fig. 15). Acute hemorrhage is important to identify, as follow-up imaging and management are affected depending upon whether the hematoma is acute or chronic. A pitfall, however, can occur when anemia leads to low attenuation of the blood along with mild atherosclerotic change leading to apparent high attenuation in the wall. In this scenario, however, the wall is affected equally in its circumference and also longitudinally, as opposed to the intramural hematoma.

Whether the aorta is involved by focal dissection, penetrating aortic ulcer, or intramural hematoma with or without associated dissection, or penetrating ulcer, the presence of these abnormalities in the ascending aorta requires immediate clinical attention, and these are commonly repaired surgically so that complications of the coronary artery compromise and pericardial tamponade can be avoided. Aneurysmal dilatation and rupture are delayed complications that can occur with aneurysm, dissection, intramural hematoma, or penetrating atheromatous ulcer. Continued surveillance by imaging after acute presentation is thereby performed.

FDG PET activity in association with atherosclerotic changes in the thoracic aorta is a common finding (43). Uptake is probably mediated by the foam cell/macrophages associated with atherosclerosis (44). However, the clinical significance of FDG PET in association with atherosclerotic changes has not been established. Some

findings suggest that FDG uptake may be associated with an active atherosclerotic process, while calcification reflects a more stable disease (43). Supporting this notion is work that shows that the HMG-CoA reductase inhibitors, lipid-lowering drug therapy decreased FDG uptake in aortic plaque (45). In addition, attempts to estimate the atherosclerotic burden in the aorta using the product of the wall thickness and the SUV have been made with a correlation between the atherosclerotic burden and patient age (46).

Vasculitis is an entity that can lead to diffuse abnormality throughout the aorta and affect the pulmonary arteries. PET imaging in arteritis manifests typically as increased uptake in the wall of the affected vessel. In terms of specific entities, Takayasu's arteritis is an arteritis typically affecting young females. The arteritis can affect the aorta and great vessel branches in addition to the pulmonary arteries. The abdominal aorta can be affected. A pre-pulseless phase can occur in which the individual is systemically ill with symptoms of fever, elevated erythrocyte sedimentation rate, myalgias, and weight loss. The post-pulseless phase can manifest with decreased pulses in the extremities related to stricturing, angina, and syncope (47). On imaging, circumferential thickening of the wall occurs in the early phase without vessel caliber change. Enhancement of the wall occurs particularly demonstrated on MRI with gadolinium contrast administration. Later focal areas of narrowing and occlusion, in addition to aneurysmal dilatation, can occur (47).

Giant cell, also termed temporal arteritis, typically affects the medium-sized arterial vessels. The aorta, however, can be affected (Fig. 16). The vessels involved are similar to the other vasculitides thickened in the circumference with possible enhancement. Other less common forms of arteritis that can affect the aorta, include ankylosing spondylitis, rheumatoid arthritis, syphilis, and Behcet disease.

A number of congenital aortic arch variants can occur. The most common is the left arch with aberrant right subclavian. A diverticulum of Kommerell can occur at the origin of the aberrant right subclavian artery, which can be aneurysmal (Fig. 17). Double aortic arch and right arch with aberrant subclavian artery are also variants in the aortic anatomy.

Lymphoma

A large anterior mediastinal mass can occur with lymphoma, with thoracic involvement occurring more commonly with Hodgkin's disease than non-Hodgkin's lymphoma (NHL)(48). Anterior mediastinal and internal mammary lymphadenopathy is more common in patients

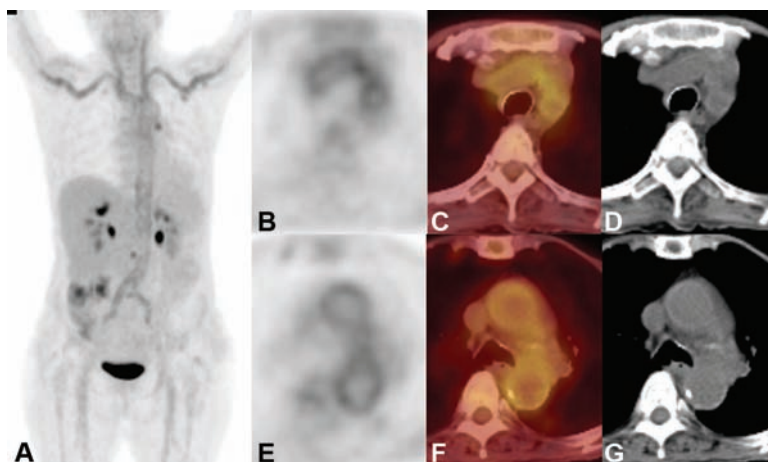


Figure 16 Temporal arteritis. PET/CT performed in an 82-year-old woman with a history of breast cancer and a new pulmonary nodule. Anterior MIP from (A) a PET/CT demonstrates mildly increased uptake throughout the walls of the major arteries in the chest and the abdomen. Transaxial slices from the PET, fused, and CT (B–D) images at the level of the innominate and left subclavian arteries show increased uptake in the walls of the vessels. At a slightly lower level below the aortic arch (E–G), rim-like metabolic uptake is seen fusing to the wall of the ascending and descending thoracic aorta. Left temporal artery biopsy showed inflammation of the media and adventitia with intimal thickening consistent with temporal arteritis.

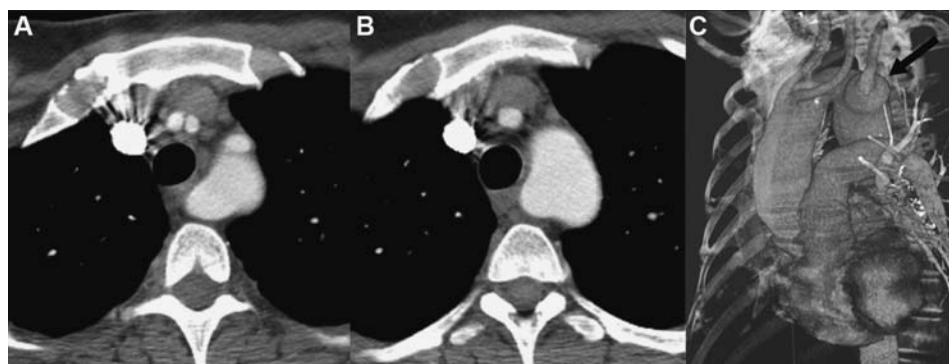


Figure 17 Diverticulum of Kommerell. Axial contrast enhanced CT scans (A,B) demonstrate a contrast-enhanced focal opacity arising off of the distal left-sided aortic arch (A) consistent with an aberrant left subclavian artery, which typically passes posterior to the esophagus and trachea. The origin (B) is termed a diverticulum of Kommerell, which may become aneurysmal. A similar diverticulum of Kommerell (arrow) can occur with a right-sided arch and aberrant left subclavian artery when non-mirror image symmetry is present, as demonstrated on this volume rendered reconstruction (C).

with Hodgkin's disease (Fig. 18) but may also be seen with some frequency in breast cancer (Fig. 19). Posterior mediastinal lymphadenopathy is much more common with NHL than Hodgkin's disease (48).

Pericardial Cyst

Pericardial cysts occur in the region of the pericardium and are lined with mesothelial cells similar to the pericardium. Contents are typically fluid attenuation without the proteinaceous material that can occur with bronchogenic cysts. These lesions may change in shape and have a

thin, close to imperceptible, wall without enhancement. The typical location for this lesion is in the right anterior pericardiophrenic angle (Fig. 20).

Bronchogenic Cyst

Bronchogenic cyst is an entity within the spectrum of bronchopulmonary foregut malformations. Pathogenesis is felt to be related to the isolation of a portion of the developing tracheobronchial tree from the remaining airways in utero. The walls of bronchogenic cysts are, therefore, composed of tissues comprised in the airways,

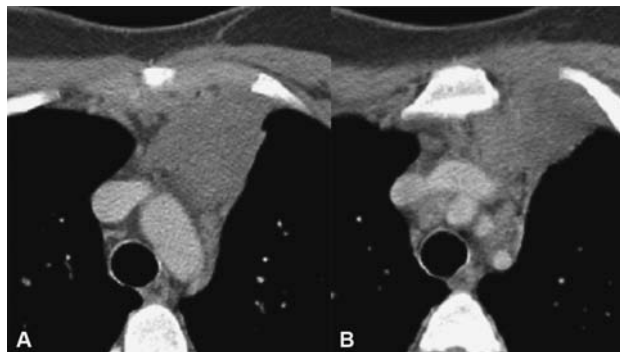


Figure 18 Anterior mediastinal Hodgkin's disease. A 23-year-old with newly diagnosed Hodgkin's disease. (A) The transaxial CT scan shows the rather homogeneous anterior mediastinal mass with additional clearly enlarged lymph nodes in the left prevascular space and more superiorly (B) in the pretracheal and bilateral paratracheal regions.

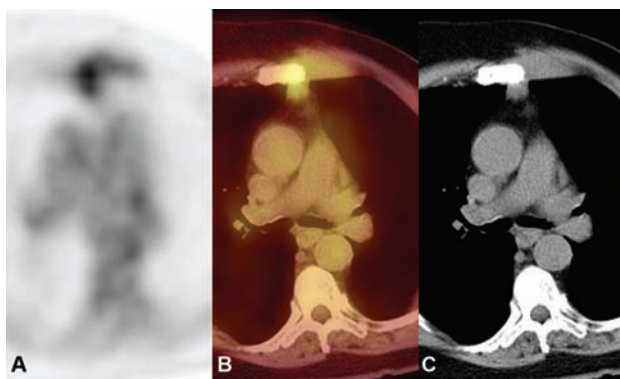


Figure 19 Internal mammary lymphadenopathy. A 77-year-old woman with a history of breast cancer treated 6 years earlier. The FDG PET/CT was performed because her tumor markers had risen. (A) PET, (B) fused PET/CT and (C) corresponding CT shows increased uptake in the soft tissue plastered against the sternum and extending to the left where there is localized thickening of the chest wall soft tissue consistent with left internal mammary lymphadenopathy.

such as cartilage, musculature, and bronchial mucosa. These lesions tend to occur in the mediastinum although approximately 10% of the time an intrapulmonary location is frequent. Subcarinal followed by paratracheal locations in the mediastinum are most frequent. In the lung parenchyma, the lower lobes medially are most frequent. Other mediastinal locations have been described including posteriorly.

On FDG PET, bronchogenic cysts are expected to be photopenic (Fig. 21) (49). A bronchogenic cyst should be considered when a well-circumscribed abnormality con-



Figure 20 Pericardial cyst. Axial CT demonstrates a well-circumscribed pericardial cyst containing fluid-attenuation lesion and located in the pericardial fat (arrow).

tains attenuation greater than that of soft tissue, approximately 50 HU or greater. The high attenuation is attributed to milk of calcium that can occur in these cysts in addition to proteinaceous material. Attenuation similar to fluid would also be suggestive. When soft-tissue density is present, postcontrast imaging would confirm a lack of enhancement and help differentiate a cystic lesion from other soft tissue lesions. In this scenario, MRI may be particularly useful for confirming a lack of enhancement in addition to identifying proteinaceous contents, which can be of high signal intensity on T1- and T2-weighted sequences, depending upon the protein content.

Esophageal and Paraesophageal Lesions

Leiomyomas, esophageal duplication cysts, and cancer can cause focal masses in the mediastinum. Leiomyomas are rare in comparison with esophageal cancer and comprise about less than 0.1% of esophageal tumors. These benign lesions are derived from mesenchymal tissue and are intramural, comprising smooth muscle and have been noted with sizes ranging from 0.2 to 17 cm, with a mean of 3.7 cm (50). The typical location is in the distal and mid-esophagus in over 90% of the cases (50). On imaging, the lesions may be centered in the wall of the esophagus with a smooth, discrete, rounded contour (Fig. 22). Attenuation is that of homogeneous soft tissue, with calcification occurring only in 9% of the cases in one series (50). Increased uptake has been described in a case recently on FDG PET with an SUV of 4.9 (51). Therefore, the CT morphology may prove helpful for identifying this entity. The lesions are enucleated or resected. Leiomyosarcomas are much less common than leiomyomas (52).

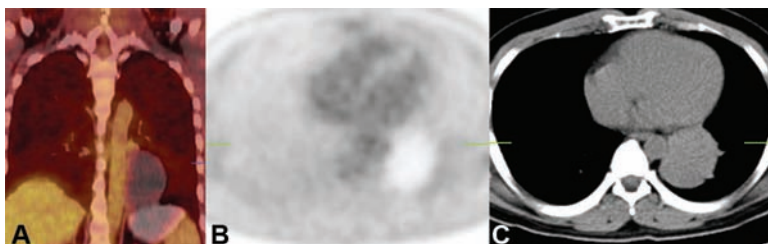


Figure 21 Bronchogenic cyst. A 36-year-old man with a mediastinal mass identified on non contrast CT. (A) Coronal image from the PET/CT and (B) transaxial PET, and (C) noncontrast CT acquired as part of the PET/CT show a metabolically inactive mass in continuity with the left hilum. A diagnostic chest CT with intravenous contrast showed no enhancement. At surgery, this was a cyst lined with benign respiratory epithelium with lobules of tracheal cartilage and endobronchial glands, i.e., a pathologically proven bronchogenic cyst.

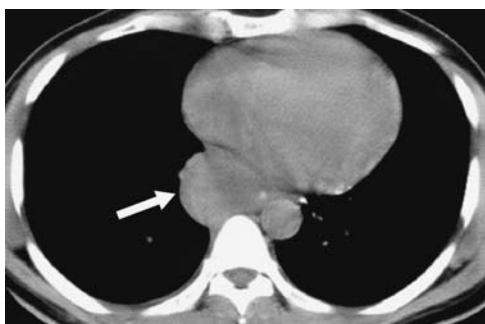


Figure 22 Esophageal leiomyoma. Exophytic well circumscribed soft tissue density (*arrow*) is eccentrically located in relation to the esophageal lumen which has a small amount of oral contrast within. There is a broad base of contact suggestive of a location within the wall of the esophagus.

Esophageal duplication cysts are part of the spectrum of bronchopulmonary foregut malformations. Typically, esophageal duplications occur adjacent to or within the wall in the distal esophagus like the leiomyoma; however, they have fluid attenuation. Cystic qualities can be confirmed by lack of enhancement with MRI. Hemorrhage or perforation of the cyst can occur when, rarely, ectopic gastric mucosa is present (25). The PET characteristics of these have not been described.

Ascites and varices can occur in the paraesophageal region. On noncontrast CT, varices are difficult to differentiate from mediastinal lymph nodes. Consideration should be made of varices in a patient with evidence of ascites and portal hypertension to avoid misdiagnosis as enlarged lymph nodes (Fig. 23). Ascites can herniate through the diaphragmatic hiatus for the esophagus and mimic a cystic lesion, however, is typically contiguous with the ascites below.

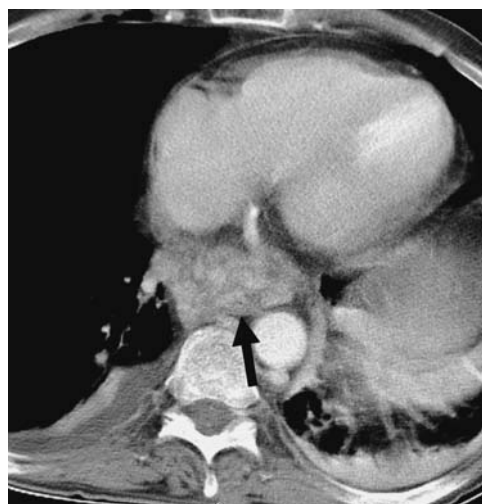


Figure 23 Paraesophageal varices. Contrast enhanced chest CT demonstrating multiple enhancing vessels adjacent to the esophagus (*arrow*). These can be confused for nodes on a noncontrast CT study.

Neurogenic Tumor

Neurogenic lesions are categorized into nerve sheath tumors, sympathetic ganglia tumors, and paragangliomas. Peripheral nerve sheath tumors are by far the most common, comprising neurofibromas and schwannomas, which can be indistinguishable on imaging. Schwannomas are encapsulated tumors derived from nerve sheath cells, while neurofibromas are unencapsulated and comprise nerve sheath cells in addition to nerve fibers and fibroblasts (53). Plexiform neurofibromas are variants that infiltrate a large portion of the nerve or plexus (53). Neurofibromas and schwannomas are both associated with neurofibromatosis I and II.



Figure 24 Neurofibromas in a patient with NF-1. (A,B) Lesions on noncontrast CT sections are well circumscribed in the costovertebral region. These tumors can be low attenuation and located along any nerve. *Abbreviation:* NF, neurofibromatosis.

Peripheral nerve sheath tumors on imaging are typically well circumscribed, round, and located in the costovertebral junction region (53). Nerve sheath tumors, however, can occur at any location where there are nerves and can occur adjacent to the ribs and in the mediastinum. Involvement of the neural foramina and spine can ensue, and the presence of the extraspinal and spinal components leads to a “dumb bell” appearance (Fig. 24). Remodeling or erosions of the adjacent ribs and vertebral bodies can be identified in approximately half of the cases. Calcifications are occasionally, although not commonly, detected. Typically, lesions are soft tissue in attenuation on non-contrast CT with low-attenuation areas corresponding to areas of low cellularity, cystic change, and lipid within myelin. Homogeneous, heterogeneous, or peripheral mild enhancement occurs after contrast administration (54). Malignant tumors of nerve sheath tumors are spindle cell sarcomas that arise typically from a plexiform neurofibroma and rarely from transformation of a schwannoma (53). On MRI, these lesions are high signal intensity on T2-weighted imaging (WI) and enhance after gadolinium administration on T1-WI. Aggressive features such as destruction of adjacent osseous abnormalities, in addition to size greater than 5 cm, raise suspicion for this rare entity. While there is an overlap in SUV between benign neurofibromas and malignant nerve sheath tumors on FDG PET, the malignant tumors do tend to have higher SUVs (55). Some findings suggest that as SUV on FDG PET increases, the prognosis for patients with malignant nerve sheath tumors worsens (56).

Schwannomas are known to be FDG PET-avid (57,58) and have been reported in the mediastinum (3,59). FDG PET may be helpful for surgical planning (60), but will not be helpful in differentiating benign from malignant neurogenic tumors, since benign schwannomas have been reported to be very active metabolically (58,59,61). In

fact, a malignant schwannoma has been reported to show only mild to moderate uptake (62).

Ganglioneuromas, ganglioneuroblastoma, and neuroblastoma are derived from the sympathetic chain ganglia and felt to represent a spectrum of biologic behavior and histology. Ganglioneuromas are benign lesions typically diagnosed in adolescents to young adults while neuroblastomas occur in children aged less than two years and are highly malignant; ganglioneuroblastoma affects patients of ages between those affected by ganglioneuromas and neuroblastomas. Only mild FDG uptake has been reported (63). Ganglioneuroblastomas are malignant lesions that are intermediate in behavior.

CT imaging of ganglioneuroma reveals an oblong tumor aligned longitudinally along the spine across multiple rib interspaces, typically positioned more anterior to the spine than the schwannoma or neurofibroma (Fig. 25). Calcification is also more frequent than with nerve sheath tumors, particularly with neuroblastoma. Enhancement on CT can be homogeneous or heterogeneous. Aggressive destruction, displacement, and infiltration of adjacent structures are suggestive of neuroblastoma or ganglioneuroblastoma, which may have hemorrhage and necrosis. Neuroblastomas are FDG-avid (64) and FDG PET has been particularly useful in identifying soft tissue and bone metastases from neuroblastoma. The sensitivity of FDG PET equals that of MIBG, although sometimes with differences in intensity of uptake between the two tracers (65,66).

Hematopoietic Tissue

Extramedullary hematopoiesis is an entity with characteristic findings of paraspinal masses associated with diffuse

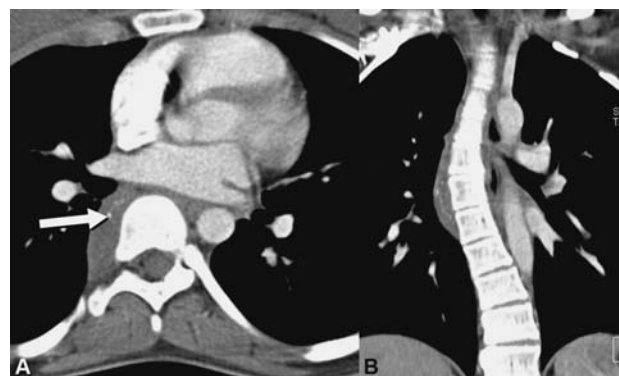


Figure 25 Ganglioneuroma. A 17-year-old female underwent CT scan for a paraspinal soft tissue mass. There is a scoliosis and a soft tissue mass lateral to the right aspect of the vertebral bodies (A,B). (A) The calcifications (arrow) (A) and longitudinal craniocaudal extent (B) are suggestive of a sympathetic chain tumor. Scoliosis is present, which may be related to the chronic mass.

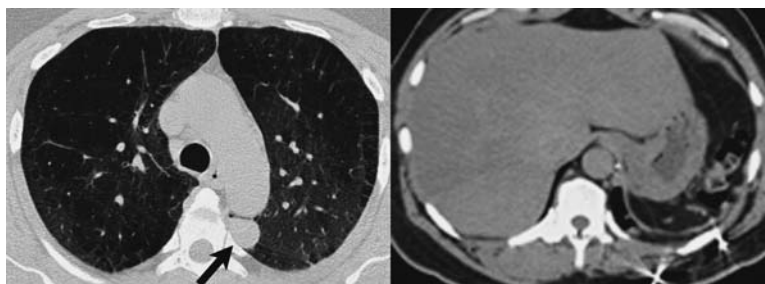


Figure 26 Splenosis. Patient with history of past trauma to the left upper quadrant with subsequent splenectomy had CT scan, which demonstrated soft-tissue densities in the periphery of the left lung (*arrow*), including one adjacent to the posterior mediastinum. Biopsy of one of these pleural lesions confirmed diagnosis of splenosis.

bone abnormality related to bone marrow expansion. Extramedullary hematopoiesis occurs in patients with long standing severe anemia such as beta thalassemia and sickle cell disease.

Splenosis can occur in the left hemithorax when trauma to the diaphragm and spleen enables fragments of spleen to enter into the thorax to lie typically in the pleural space abutting the mediastinum (Fig. 26). Consideration of this entity is helpful when there are peripheral nodular densities in the periphery of the thorax with evidence of left upper quadrant trauma. Integrity of the diaphragm is best assessed on coronal imaging.

SUMMARY

1. FDG-PET imaging has a limited role in identifying the specific etiology of a mediastinal lesion. In the scenario of abnormal uptake, CT morphology and location of the lesion is helpful for developing major differential considerations. Nonetheless, when there is malignancy, FDG PET will be useful in identifying the extent of disease.
2. Thymic hyperplasia preserves the normal anatomy of the thymus as opposed to a thymic mass. It is most commonly encountered in the oncologic patient after chemotherapy. While this entity is more common in children and young adults, it can occur in more mature adults, and it may persist for well over a year after the cessation of therapy.
3. Teratoma is suggested when there is fat, calcification, and fluid.
4. Thymoma can be locally invasive with distant spread early on being less common. FDG uptake tends to increase with aggressiveness of the lesion and can be used to differentiate thymoma from thymic carcinoma. PET/CT is also useful for staging of thymic neoplasms in which metastases can occur almost regardless of histology.
5. Lymphoma can present in the anterior mediastinum as a large mass and is suggested by the presence of multicompartiment involvement and multiple soft tissue densities within the large mass. Additional lymphadenopathy will increase confidence in this diagnosis.
6. Vascular etiologies need to be considered on a non-contrast CT particularly when a heterogeneous soft tissue mass is identified. Contrast CT may therefore be indicated. FDG PET may identify active atherosclerosis and vascular inflammation. The activity that is associated with these vascular lesions on PET/CT may resolve with therapy.
7. While schwannomas and neuroblastomas are expected to be FDG PET-avid, the uptake in ganglioneuromas is reported to be less although the literature is very limited regarding the last. FDG PET may be helpful in assessing malignant degeneration of neurofibromatosis.

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8

Diseases of the Lungs and Pleura: FDG PET/CT

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LUNG AND PLEURA: NORMAL PET UPTAKE, CT ANATOMY, AND POTENTIAL PITFALLS

Several normal structures in the thorax demonstrate varying degrees of 18-fluorodeoxyglucose (FDG) uptake that can be misinterpreted as pathology. The causes of false-positive FDG positron emission tomography (PET) interpretations relate to the lung parenchyma, the heart, glandular breast tissue, esophagus, and the thymus. Additionally, to avoid missing low activity pathology, an understanding of the computed tomography (CT) anatomy, particularly on noncontrast CT, is essential. A detailed description of the entire thoracic CT anatomy is beyond the scope of this section; and therefore, focus will be placed on areas that are most problematic for interpretation.

Normal PET Uptake

Thymus

The thymus appears as a discrete structure in children and young adults (1). The size of the gland decreases gradually after puberty and by 40 to 50 years of age is composed primarily of fatty tissue in older patients. Mild FDG uptake

can be associated with normal thymic tissue children, adolescents, and younger adults. In these cases, uptake in an “inverted Y” configuration will fuse to a bilobed soft tissue structure in the anterior mediastinum that maintains a triangular configuration and size appropriate for patient age.

Homogeneous low uptake of 18-FDG in lung tissue can occur on attenuation corrected images most often at the lung bases because of respiratory motion activity, which displaces abdominal structures such as liver and spleen in the lung fields during PET acquisition. Thus, because of discrepancies between the position of the diaphragm between the PET acquisition and the CT acquisition, “over correction” may occur.

Uptake of FDG by the heart is very variable and depends on substrate availability. In a patient who has been fasting and in whom insulin levels are, therefore, low, the predominant myocardial substrates are fatty acids, so that FDG uptake subsequently is expected to be low in comparison to when insulin levels are high. However, regardless of proper patient preparation, left ventricular wall activity is often visible even in the fasting state, likely because 30% to 40% of the energy is still

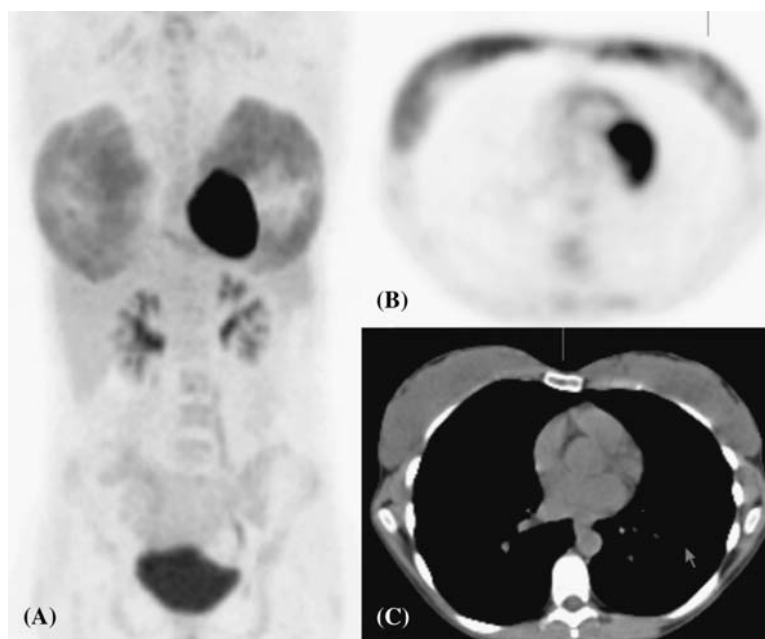


Figure 1 A 26-year-old woman with a history of lymphoma. FDG PET/CT was performed for routine monitoring for disease. She was four weeks postpartum and nursing. Anterior view from a maximum intensity projection (A) shows diffusely increased uptake in both breasts. This is also seen on a transaxial image (B) to correspond to dense lactating breast tissue on CT (C).

derived from oxidative metabolism of the glucose (2). While left ventricular activity is normally seen, it is unusual to see right ventricular activity unless there is cardiac disease affecting those chambers (3).

Breast Tissue

Glandular breast tissue normally may show moderate uptake of FDG, and this uptake may be greater in subjects taking hormone replacement therapy (4). Marked uptake is seen in lactating breasts (Fig. 1). Gynecomastia in males has been associated with increased FDG activity, e.g., in patients with prostate cancer on anti-androgen therapy and in patients with spironolactone-induced gynecomastia (5).

Esophagus

The esophagus does not usually show activity unless there is active disease. When homogeneously increased

uptake of tracer is seen along the esophagus, inflammation due to gastroesophageal reflux disease or infection should be suspected. Intensity may range from mild to moderate reflecting the severity of inflammation. Physiologic, more focally increased FDG uptake at the gastroesophageal junction is seen frequently. This is thought to be due to contraction of the lower esophageal sphincter to prevent reflux from the stomach. Given that focal uptake can be a frequent finding, differentiation between focal inflammatory change and malignant activity may be difficult.

Brown Fat

A symmetrical curvilinear pattern of intense uptake is sometimes noted in the lower neck, in the supraclavicular, and paraspinal regions (Fig. 2). Previously thought to be related to muscle spasm, this activity fuses with fatty tissue on PET/CT images as a result of metabolic activity

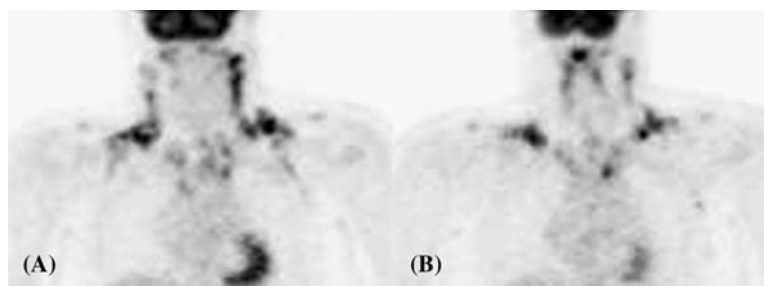


Figure 2 A 29-year-old woman with breast cancer. Coronal images of the chest and neck demonstrate increased uptake in the brown fat of the neck and supraclavicular regions extending into the axillary regions (A) as well as the superior mediastinum (B).

in brown fat (6). Brown fat is a vestigial organ of thermogenesis that is innervated by the sympathetic system. Brown fat is more frequent in female patients, in patients with a lower body mass index, and seems to be activated by cold exposure (7).

Skeletal Muscle

Skeletal muscle activity can be seen in the chest wall in patients with chronic obstructive pulmonary disease. In these patients, accessory respiratory muscles are used, resulting in increased activity in the intercostal regions (8). Skeletal muscle uptake occurs with stress in the trapezius, cervical, and paraspinal muscles. Hyperventilation may

also induce uptake in the diaphragm at the level of its insertions (9).

Bone Marrow and Other Locations

The bone marrow typically has low FDG uptake; however, uptake can diffusely and uniformly increase as a result of chemotherapy or colony stimulating factors (10,11). This may be seen in the spine and the ribs. After radiation therapy, bone marrow uptake in the area of treatment is usually decreased (Fig. 3) FDG activity can be frequently seen in the thoracic aorta and carotid vessels in the older population and has been associated with atherosclerotic plaque-related inflammation (Fig. 4) (12).

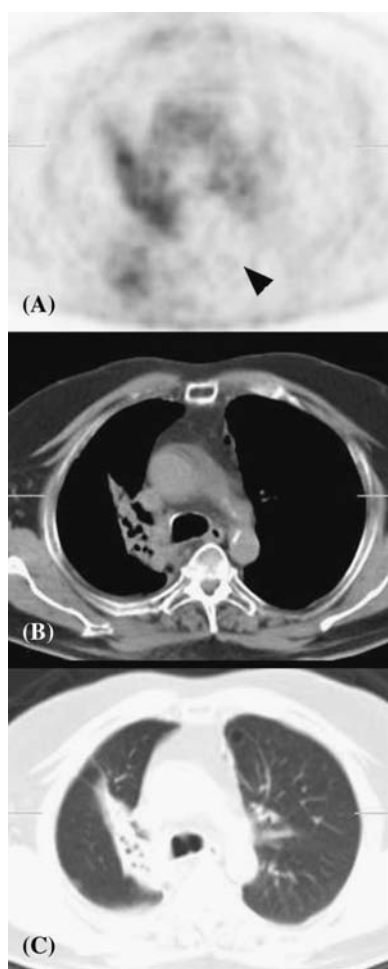


Figure 3 A 75-year-old man with a history of lung cancer and treated with radiation to the mediastinum and right hilum. FDG PET image (A) from the PET/CT and the corresponding CT with soft tissue windows (B) and lung windows (C) shows increased uptake in the area corresponding to radiation fibrosis in the perihilar lung. Also note (*arrowhead*) the absence of uptake in the marrow of the spine at this level due to radiation ablation of hematopoietic cells within the radiation port.

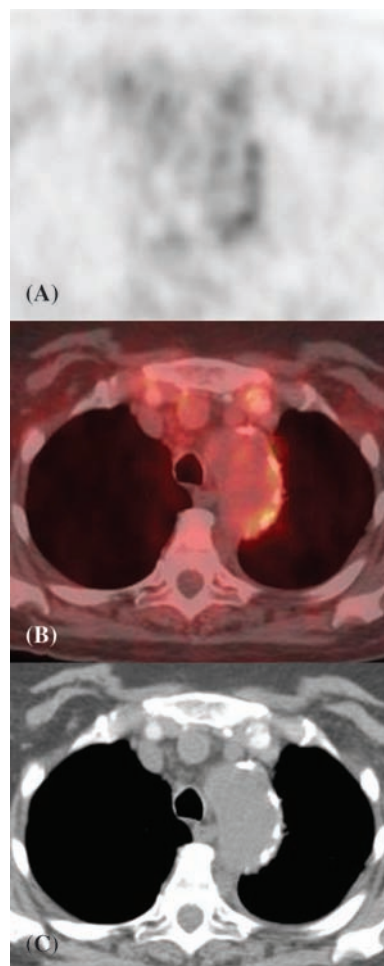


Figure 4 Atherosclerotic change in the aortic arch shows the typical curvilinear FDG uptake on PET (A) attributed to the inflammatory change, i.e., foam cells fusing (B) with ongoing atherosclerosis in the aortic arch in this patient with calcification seen in the same area on CT (C).

CT Anatomy

The Hila

The hilar structures comprise the main right and left pulmonary arteries and subsequent branches, the lobar bronchi and subsidiaries, and the pulmonary veins. Knowledge of the hilar anatomy is essential for increasing diagnosis of pathology when correlating PET activity to anatomy. In particular, an understanding of the CT anatomy will help identify the presence of findings with low FDG uptake, such as low activity nodes, congenital vascular variations, or carcinoid tumors. The identification of the hilar components is facilitated by cine interpretation.

Pulmonary veins

The pulmonary veins drain the blood from the lung parenchyma into the left atrium. Typically, in 60% to

70% of the population, four pulmonary veins are present (13). The right superior pulmonary vein drains the right upper lobe, while the right inferior pulmonary vein serves the right lower lobe. The vein draining the right middle lobe typically joins the right superior pulmonary vein before it enters into the left atrium. On the left, the left superior pulmonary vein drains the left upper lobe and the lingula, while the left inferior pulmonary vein provides venous return from the left lower lobe. The superior pulmonary veins drain anterior to the respective bronchi and pulmonary arteries. The inferior pulmonary veins have a horizontal course parallel to the axial plane into the left atrium (Fig. 5). Pulmonary vein diameter has been reported to range between 9 and 13 mm (14).

Pulmonary veins do not accompany the bronchi and vary in terms of their branching pattern. Variations in pulmonary vein anatomy relate typically to accessory

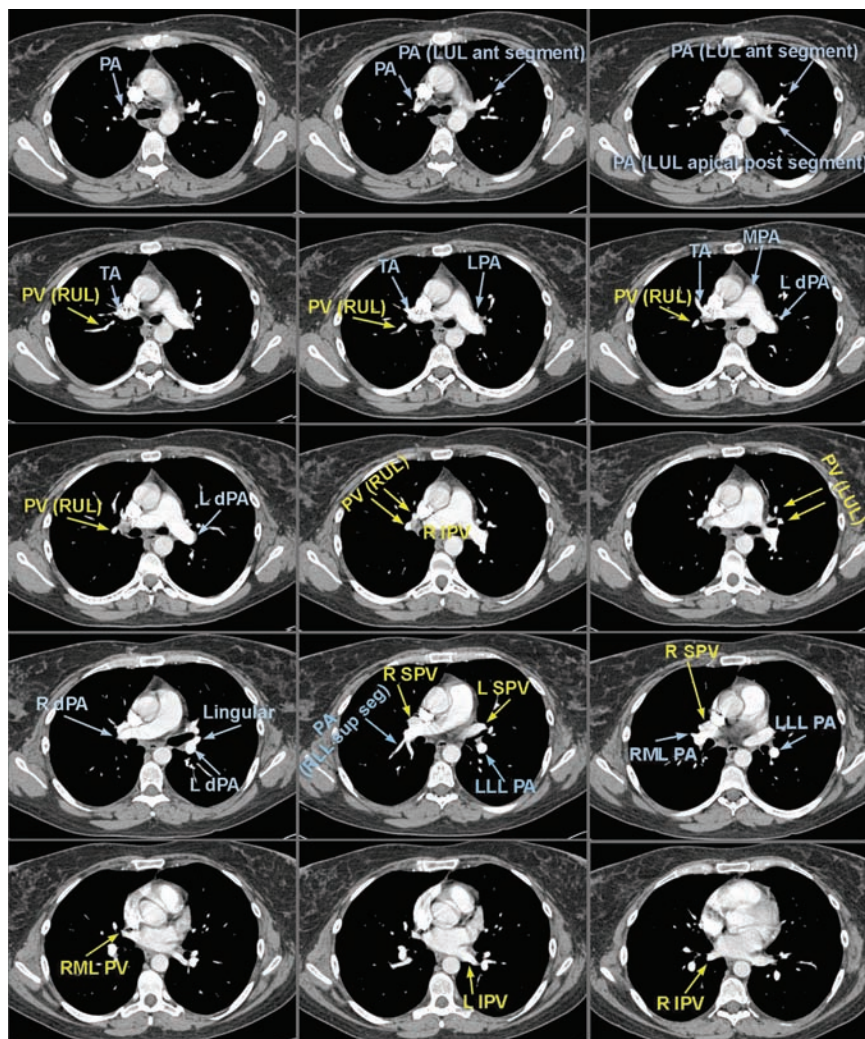


Figure 5 Pulmonary vascular anatomy: axial postcontrast CT sections through the thorax. *Abbreviations:* PA, pulmonary artery; TA, truncus anterior; LUL, left upper lobe; PV, pulmonary vein; RUL, right upper lobe; RML, right middle lobe; LLL, left lower lobe; R, right; L, left; dPA, descending (interlobar) pulmonary artery; ant, anterior; post, posterior; SPV, superior pulmonary vein IPV, inferior pulmonary vein.

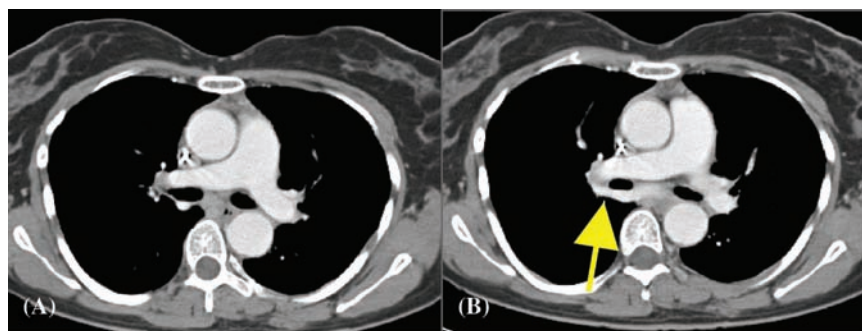


Figure 6 Variation in pulmonary vein drainage. Pulmonary vein from the right upper lobe drains into the left atrium directly after passing behind right upper lobe bronchus (A) and bronchus intermedius (B).

veins in the right lung or fewer veins in the left lung. The vein from the right middle lobe can directly enter the left atrium as an independent vessel called the right middle vein, which accounts for 55% to 93% of the accessory right-sided veins. An accessory vein from the posterior segment of the right upper lobe or from the superior segment of the right lower lobe can pass behind the bronchus intermedius and mimic a node on noncontrast CT. The vessel can directly drain into the left atrium or the right superior or inferior pulmonary veins close to the entry into the left atrium (13,15) (Fig. 6) (Table 1).

Variations in pulmonary vein drainage can occur. The superior or inferior pulmonary veins can drain into the

inferior or superior pulmonary veins, respectively. A prominent soft tissue area in the hilum on noncontrast CT, therefore, may result and serve as a pitfall if misinterpreted as pathology (16,17) (Figs. 7, 8). Additionally, anomalous pulmonary venous drainage to a systemic vessel such as the superior vena cava of the left subclavian vein can occur.

Pulmonary arteries

The main pulmonary artery originates at the pulmonic valve and courses distally to supply blood to the lung parenchyma. The right and left pulmonary arteries arise from the main pulmonary artery. Typically, the bronchi

Table 1 Right and Left Lung Major Anatomical Components

	Right lung	Left lung
Lung segments with respective bronchi	Right upper lobe: apical, posterior, anterior Right middle lobe: lateral, medial Right lower lobe: superior, medial-basal, anterior-basal, lateral-basal, posterior-basal	Left upper lobe and lingula: Apical posterior, anterior; Superior and inferior (lingular) Left lower lobe: anteromedial-basal, lateral-basal, posterior-basal
Pulmonary arteries	Right pulmonary artery Truncus anterior Apical (RA1) Posterior (RA3)—frequently arises from interlobar Anterior (RA2) Interlobar artery Middle lobe Lateral (RA4) Medial (RA5) Lower lobe Superior (RA6) Medial-basal (RA7) Anterior-basal (RA8) Lateral-basal (RA9) Posterior-basal (RA10)	Left pulmonary artery Interlobar artery Left upper lobe Upper division Apicoposterior (LA1 + LA3) Anterior (LA2) Lingular division Superior (LA4) Inferior (LA5) Lower lobe Superior (LA6) Anteromedial-basal (LA7+8) Latera-basal (LA9) Posterior-basal (LA10)
Lobar drainage by pulmonary veins	RUL via superior pulmonary vein RML via vein that joins superior pulmonary vein prior to entry into the right atrium RLL via the inferior pulmonary vein	LUL and lingula via the superior pulmonary vein LLL via the inferior pulmonary vein

Source: From Refs. 18,579, and 580.

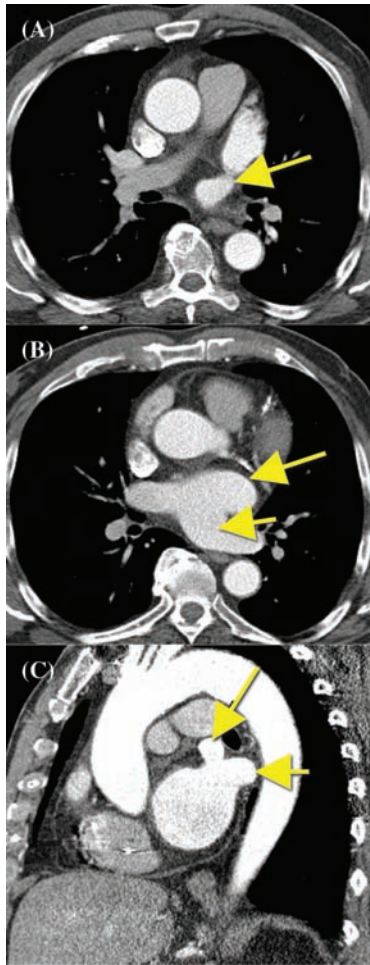


Figure 7 Variation in pulmonary venous drainage. Axial sections (A and B) and left anterior oblique multiplanar reconstruction (C) demonstrate the left inferior pulmonary vein (*short arrow*) joining the left superior pulmonary vein (*long arrow*) at the superior aspect of the left atrium. Right superior pulmonary vein drains into the left atrium at a location close to the orifice of the left superior pulmonary vein.

are accompanied by a pulmonary arterial branch. The pulmonary arterial system has many variations in the branching pattern at the lobar, segmental, and subsegmental regions. Additionally, small accessory pulmonary arterial branches can occur.

The right pulmonary artery gives rise to the truncus anterior and interlobar artery. The truncus anterior carries blood primarily to the anterior and apical segments of the right upper lobe. A posterior right upper lobe is often supplied by a branch that arises from the interlobar artery. The descending, or interlobar, artery after its origin from the right pulmonary artery courses inferiorly and bifurcates into the pulmonary arteries to the right middle and lower lobes. Most typically, the right middle lobe pulmonary artery derives from the interlobar artery (Fig. 5) (Table 1) (18).

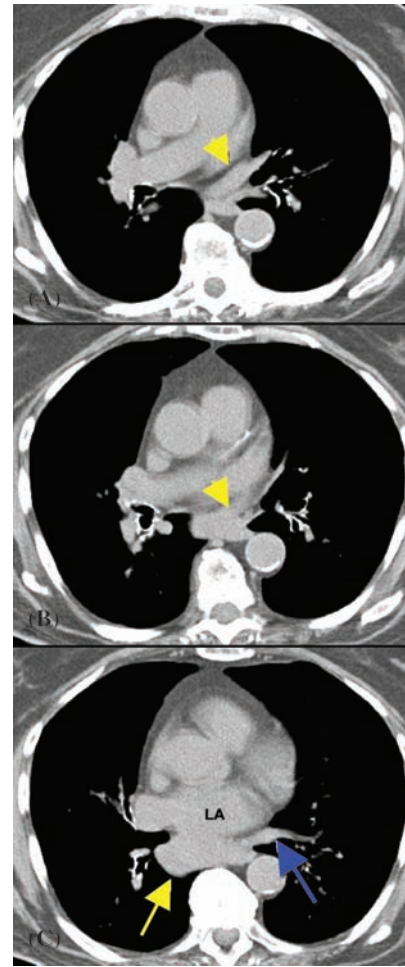


Figure 8 Variation in pulmonary vein drainage: left superior pulmonary vein (*arrowhead*) (A,B) is confluent with a soft tissue density behind the heart (C), which represent a common confluence (*yellow arrow*) of the left inferior (*blue arrow*) and right inferior pulmonary vein. The single vascular structure drains into the left atrium. *Abbreviation:* LA, left atrium.

Variation occurs in the branching of the pulmonary arteries. The left pulmonary artery has an ascending portion, before it becomes the interlobar pulmonary artery once it passes over the left mainstem bronchus and begins to descend caudally. A large amount of variability exists in the branching pattern of the left pulmonary arterial system. Branches supplying the segments of the left upper lobe typically arise from the interlobar artery proximally, although branches to the left upper lobe can arise as a common trunk from the pulmonary artery similar to that of the right-sided truncus anterior. The branch of the pulmonary artery to the lingula typically arises more caudally off of the interlobar artery than those supplying the superior aspect of the left upper lobe. (Fig. 5) (18).

The main pulmonary artery typically measures up to 28 to 30 mm in diameter, as measured 1 cm proximal to the bifurcation of the right and left pulmonary arteries. On average, the main pulmonary artery has dimensions of 24.2 ± 2.2 mm (19) (mean ± 1 standard deviation) and 28 ± 7 mm (mean ± 1 standard deviation) (20). The proximal right pulmonary artery measured in the study by Kuriyama is 18.7 ± 2.8 mm (mean ± 1 standard deviation) in diameter, and the left pulmonary artery 21.0 ± 3.5 mm (mean ± 1 standard deviation) (19).

Hilar nodes

Hilar nodes appear as soft tissue, typically nonenhancing findings on contrast-enhanced CT in comparison with the adjacent vasculature. They are not as easily identified on CT performed without the administration of intravenous contrast. Hilar nodes lead to an enlargement of the hilar regions in a lobulated manner, in which focal convexities fail to give rise to a pulmonary arterial branch. Dimensions of hilar nodes are typically on the order of 3 mm in short axis (21). Right hilar nodes larger than 10 mm and left hilar nodes greater than 7 mm in short axis are considered abnormal (22) (Fig. 9). Additionally, adenopathy is suspected when soft tissue is located posterior to the bronchus intermedius. The posterior wall of right upper lobe bronchus normally abuts the lung and is imperceptible on soft tissue windows.

While normal mediastinal lymph nodes are expected to demonstrate no FDG accumulation, mild hilar lymph node activity is often seen. Usually, this is the same intensity as the uptake in normal structures in the mediastinum (Fig. 10); however, on occasion, hilar lymph nodes may demonstrate more intense activity. Neither normal standardized uptake values (SUVs) for hilar lymph nodes have been established nor target to background ratios for intensity of uptake. While focal uptake in hilar nodes above the intensity of the mediastinum must be viewed with suspicion, anthracotic changes and inflammatory disease such as sarcoid may explain this increased uptake also (Fig. 10).

Airways

An understanding of airway branching and their variations is helpful for localizing and accurate reporting of pathology. Careful review of the airways on the CT component of PET/CT is useful for identifying endobronchial lesions that show little or no metabolic activity. Some endobronchial abnormalities require attention such as carcinoid tumors while others are benign, like secretions. A detailed description is beyond the scope of this text, and reference to dedicated texts toward CT in this area will provide more in depth coverage of this topic.

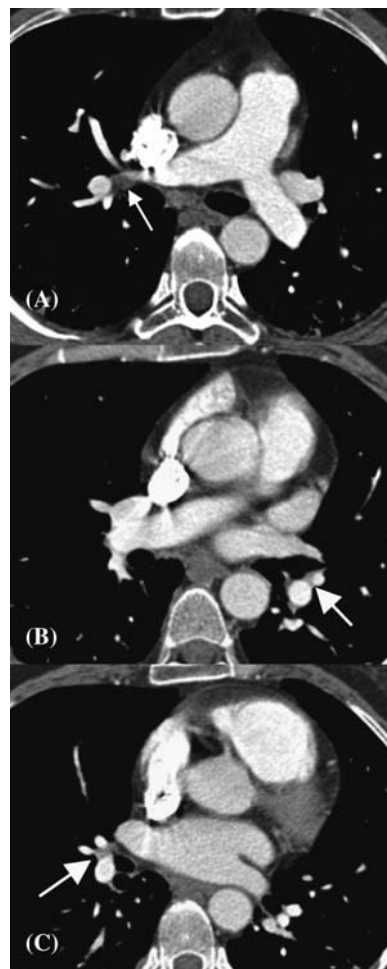


Figure 9 Common locations for hilar nodes (arrows) in the right hilum (A,C) and left hilum (B).

The trachea begins at the cricoid cartilage and ends at the carina, where it gives rise to the right and left mainstem bronchi. The intrathoracic portion of the trachea begins at the level of the manubrium. The trachea typically contains horseshoe-shaped cartilaginous rings with a posterior membranous portion. Therefore, the trachea upon inspiration appears horseshoe-shaped anteriorly and flat in the posterior portion. During expiration, the posterior wall of the intrathoracic trachea moves anteriorly a small degree, with mild decrease in the anterior posterior dimension. Upon forced expiration, the tracheal membrane invaginates anteriorly to a greater degree, at which time the trachea appears crescentic in shape with decrease in the anterior posterior dimension. As shown by Stern et al. in normal patients undergoing forced expiration, the anterior posterior trachea dimension decreases by an average of 32% (23), while the medial lateral diameter decreases by 13%.

The right mainstem bronchus bifurcates into the right upper lobe bronchus and the bronchus intermedius.

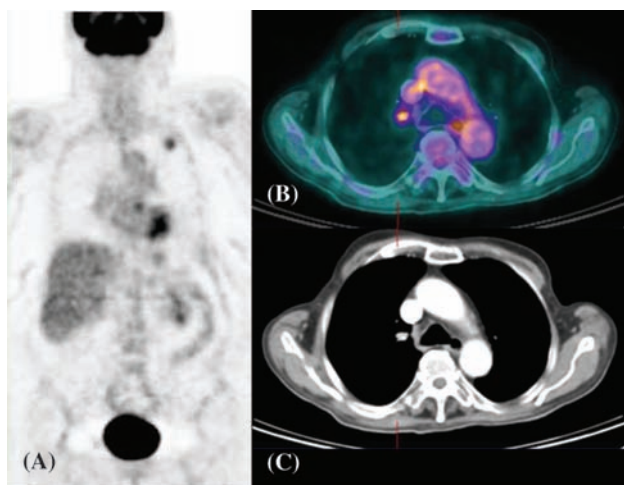


Figure 10 Normal and false-positive hilar lymph nodes on PET. (A) Coronal PET image in a patient with a newly discovered pulmonary nodule shows normal intensity hila. Axial fused (B) and CT (C) views from a PET/CT performed in a different patient with a smoking history and right upper lobe lung nodule (not shown). PET/CT showed increased uptake in a right, partially calcified lymph node measuring approximately 1.2 cm in maximal dimension. This was subsequently biopsied and showed lymphocytic infiltrate along with focal fibroblastic proliferation and coal dust particles related to anthracosilicosis.

In comparison with its left-sided counterpart, the right mainstem bronchus is short. The course of the right upper lobe bronchus is oriented within the transverse axial plane (Fig. 11). The right upper lobe anterior and posterior segmental bronchi are seen typically in the same axial section, while the apical segment is visualized in cross section at more superior levels. The bronchus intermedius branches into the right middle and lower lobe bronchi, at which a small spur is located in the right lateral aspect of the airways. The right lower lobe superior segmental bronchus is seen as a tubular structure coursing posteriorly from the right lower lobe bronchus in the axial plane and arises at the same craniocaudal level as the right middle bronchus. The truncus basalis, formed after the takeoff of the superior segmental bronchus, first gives rise to the medial basal bronchus and subsequently the anterior-, lateral-, and posterior-basal bronchi.

The left mainstem bronchus is longer and has a more downward angled orientation as compared with the right mainstem bronchus. The branching of the left mainstem bronchus into the upper and lower lobe bronchi occurs at a “second carina” in the lower portion of the left upper lobe bronchus. The lingular bronchus and the subsequent superior and inferior lingular segmental airways originate off of the inferior aspect of the left upper lobe bronchus. The bronchi to the upper aspect of the left upper lobe arise

from the superior aspect of the left upper lobe bronchus. The upper aspect of the left upper lobe comprises the apical posterior and the anterior segments, which have respectively named bronchial supply. As on the right, the left lower lobe bronchus branches into a superior segmental bronchus and a truncus basalis. The left lower lobe consists of the superior segment and the three basilar segments (anterior-medial, lateral-, and posterior-basal segments), which are supplied by segmental bronchi with the same name (Fig. 11) (Table 1).

At the segmental level and more distally, the branching pattern of the bronchi can vary. As examples, the anterior-medial, lateral-, and posterior-basal bronchi may not originate from the truncus basalis at one time, but rather a common bronchus and a segmental bronchus may arise from the truncus basalis, and then the common bronchus subsequently splits into two segmental bronchi. Additionally, the apical segmental bronchus of the right upper lobe may arise from either the anterior or posterior segmental bronchi rather than at a trifurcation from the right upper lobe bronchus with the anterior and posterior segmental bronchi.

Mediastinal Nodes

The mediastinum is the space containing the heart, aorta, thymus, esophagus, lymph nodes, and nerves in the middle of the thorax. Given the large role that nodal assessment has in lung cancer staging, attention will be directed toward review of the normal appearance of mediastinal lymph nodes. Additionally, structures that can be mistaken as lymph nodes will be covered, and focus will be placed on how to avoid pitfalls and misdiagnosis (Table 2). The nomenclature for nodal locations will be discussed in the lung cancer staging section with emphasis placed on the anatomic landmarks for labeling of mediastinal nodes.

The presence of increased FDG PET activity in a mediastinal lymph node regardless of size anywhere in the mediastinum should raise suspicion of pathology. However, increased uptake may not definitively identify malignant involvement, since inflammatory change can also cause this.

When evaluating mediastinal nodes on CT, size is the main criteria used for identifying abnormal nodes. Normally, mediastinal nodes range up to 1 cm in short axis dimension (22), are typically ovoid in shape, and can contain a hilus measuring the attenuation of fat. In some locations, lymph node enlargement should be considered even when lymph nodes measure less than 1 cm in short axis. In the retrocrural region, nodal size greater than 6 mm is typically considered abnormal on CT (24). Lymph nodes in the peridiaphragmatic location are considered abnormal if greater than 5 mm in short axis (25).

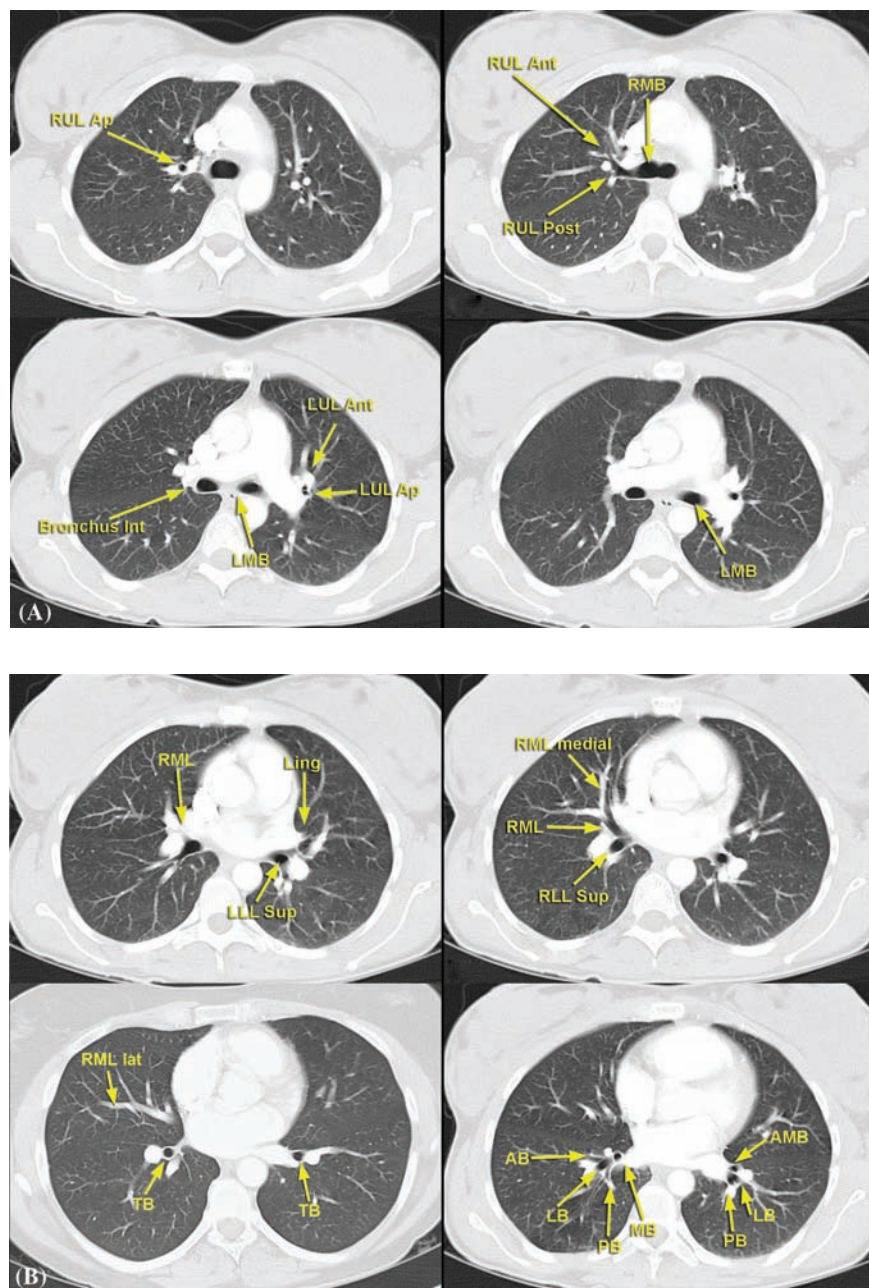


Figure 11 (A,B) Bronchial anatomy as depicted on CT scans. *Abbreviations:* RUL, right upper lobe; LUL, left upper lobe; Ap, apical; Ant, anterior; Post, posterior; RMB, right mainstem; LMB, left mainstem; Bronchus int, bronchus intermedius; RML, right middle lobe; Ling, lingular; RLL, right lower lobe; LLL, left lower lobe; TB, truncus basalis; AMB, anteromedial basal; LB, lateral basal; PB, posterior basal; MB, medial basal; AB, anterior basal.

In normal situations, mediastinal nodes in the region of the inferior pulmonary ligament are not usually visualized on CT. The inferior pulmonary ligaments are bilateral ligamentous structures that tether both lower lobes to the mediastinum. Each ligament comprises two layers of visceral and parietal pleura, and extends from the inferior aspect of the inferior pulmonary veins to the diaphragm. On CT, the ligament has a linear configuration that abuts

the mediastinum near the esophagus and its surrounding fat (26) (Fig. 12).

Vessels or other mediastinal structures can be misinterpreted as mediastinal lymph nodes particularly on non-contrast CT (Table 2). In the aorticopulmonary window region, a duplicated or left-sided superior vena cava or partial anomalous pulmonary venous return to the left brachiocephalic vein can mimic a lymph node; however,

Table 2 Normal Anatomy or Variants That Can Be Misinterpreted as Lymph Nodes**Pericardial recess**

- Subcarinal region—oblique pericardial sinus and posterior pericardial recess
- Left paratracheal region—transverse pericardial sinus
- Left periaortic or phrenic region, aortopulmonary window region—anterior portion of the superior aortic recess
- Right periaortic or phrenic region—lateral portion of the superior aortic recess
- Right paratracheal region—posterior and lateral portions of the superior aortic recess
- Inferior pulmonary ligament region—inferior pulmonary vein recess

Prominent cysterna chyli (right retrocrural region)**Vascular**

- Left prevascular, paraaortic, aortopulmonary window regions (left-sided SVC, partial anomalous pulmonary venous return from the left upper lobe)
- Posterior to bronchus intermedius (right lower lobe superior segment pulmonary vein branch)
- Hilar regions (inferior and superior pulmonary veins joining outside of left atrium)



Figure 12 Location of inferior pulmonary ligament (*arrow*). The inferior pulmonary ligament is a linear structure as seen on the left in this image. The ligament typically abuts the mediastinum near the esophagus and courses from the inferior aspect of the hilar structures to the diaphragm. In this individual, early postsurgical changes are noted posterior to this structure.

vascular entities can easily be demonstrated as a tubular structure when viewing multiple contiguous axial sections or coronal multiplanar images (Fig. 13). The cysterna chyli receives the lymphatic drainage from the abdomen and

courses craniocaudally adjacent to the azygos vein in the right paraspinal region as the thoracic duct, which eventually drains into the left subclavian vein. A prominent cysterna chyli (Fig. 13) in the retrocrural region between L2 and the inferior aspect of T11 can be mistaken as an enlarged node given its round and elliptical shape on axial imaging. Nevertheless, discrimination of these two entities is possible, as the cysterna chyli will have Hounsfield units that reflect its fluid rather than soft tissue attenuation (27,28). In a series of 403 cases by Smith et al., the cysterna chyli was identified in seven cases on 7- and 5-mm sections and averaged 7.4×7 mm (27).

Pericardial Recesses

The pericardium envelops the heart, great vessels, and pulmonary veins that enter into or exit from the heart. The pericardium consists of an outer fibrous and an inner serous layer. The serous layer comprises an outer parietal layer that lines the inner aspect of the outer fibrous pericardium and an inner visceral, also termed epicardial, layer.

The reflections of the pericardium create transverse and oblique sinuses that are located around the great vessels at the base of the heart. The sinuses are contiguous with the

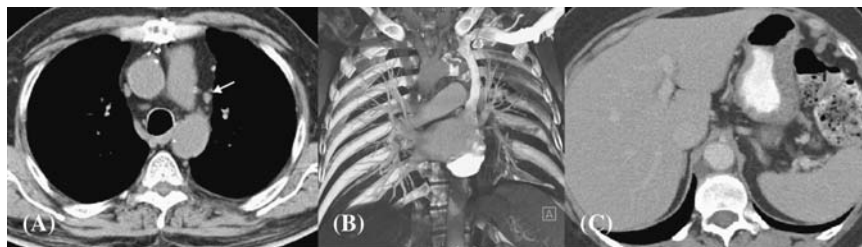


Figure 13 Potential mimickers of mediastinal nodes. Left-sided SVC. On axial CT section without contrast, a left-sided SVC can simulate a node (*arrow*) (A). However, the tubular nature, as best demonstrated on volume rendered image in the coronal plane (B), is indicative of a vasculature structure. The left-sided SVC drains into the coronary sinus. (C) A prominent cysterna chyli and thoracic duct appears as a fluid-filled rounded structure in the right retrocrural region and may be mistaken as a retrocrural node.



Figure 14 (A,B) Anterior superior aortic recess (arrowhead, B) and posterior superior aortic recess (long arrow). The posterior superior aortic recess (long arrow) often has a flat or concave border anteriorly and convex border posteriorly. (C) More caudally, the posterior superior aortic recess and left pulmonary recess (white arrowhead) of the transverse sinus (black arrow) are noted. The posterior pericardial recess of the oblique sinus is more posterior in location (white arrow).

pericardial space. The pericardial cavity and sinuses form the recesses, which are the small reflections of pericardium along the great vessels and pulmonary veins that enter and exit the heart. The transverse sinus gives rise to the superior aortic recess (divided into anterior, posterior, right lateral portions), inferior aortic recess, right pulmonary recess, and left pulmonary recess (Fig. 14). The oblique sinus gives rise to the posterior pericardial recess. The pericardial cavity proper gives rise to the postcaval recess and right and left pulmonary vein recesses.

In normal situations, fluid on the order of 20 to 25 cc is present in the pericardium. Fluid in normal and pathologic situations within the pericardial recesses and sinuses can mimic nodes, but can be differentiated by its fluid attenuation as opposed to the soft tissue density of nodes (29–36). Typically, on FDG PET, pericardial fluid is not associated with any FDG activity.

One of the most commonly identified fluid-filled recesses is the posterior portion of the superior aortic recess, termed the posterior superior aortic recess, which is one of the regions of the superior aortic recess. The superior aortic recess is divided into anterior and lateral regions in addition to the posterior component. The pos-

terior superior aortic recess abuts the posterior aspect of the ascending aorta. A “high-riding” pericardial recess has been used to describe when the posterior superior aortic recess extends more cranially than typical into the right paratracheal region between the brachiocephalic vessels and trachea, lacking a definable wall and identified in 6.6% of 21 patients in a study by Basile et al. (Fig. 15) (34,36). In a series by Groell et al., the superior aortic pericardial recess was identified in 47% of the cases (31).

Many other pericardial recesses can be visualized filled with fluid, and a full description of these has been described in the literature. Groell et al. also identified on multidetector CT scans other pericardial reflections that frequently contained fluid were the transverse sinus (95%), oblique sinus (89%), the left pulmonary recess (81%), posterior pericardial recess (67%), left pulmonary vein recess (60%), the right pulmonary recess (51%), and the right pulmonary vein recess (29%). Fluid in the pericardial recess adjacent to the inferior pulmonary vein can mimic a node in the right infrahilar region (29). The fluid tends to surround or be visualized on both sides of the inferior pulmonary vein.

LUNG PATHOLOGY

Pulmonary Nodule Assessment

Differential Diagnosis for the Solitary Pulmonary Nodule and Multiple Nodules

A pulmonary nodule has been defined as any focal abnormality with rounded contours that measures 3 cm or less. Nodules are often called small when measuring less than 1 cm. Lesions greater than 3 cm are termed masses. Difficulty exists in categorizing focal lung disease as a nodule, as opposed to other entities such as linear scarring and consolidation.

Nodules have been traditionally described as solitary or multiple. However, given the improved image quality provided by CT technology, often more than one small incidental nodule can be identified in a large proportion of individuals. In smokers, in lung cancer screening trials, Henschke et al. and Swensen et al. reported 23% and 69%

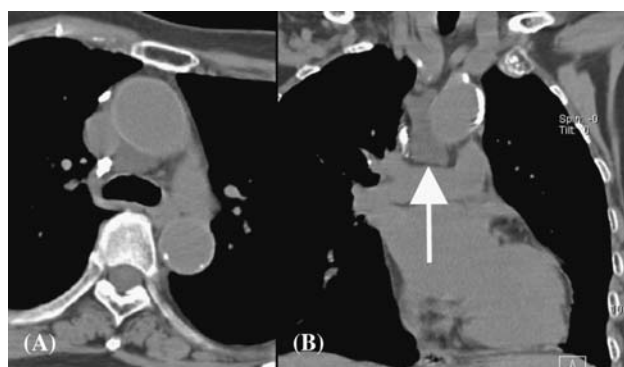


Figure 15 High riding posterior superior aortic recess. Axial CT shows posterior location behind ascending aorta (A). Coronal MPR (B) demonstrates craniocaudal dimension and the high location extending to near the superior aspect of the aortic arch (arrow).

of patients to contain small nodules, respectively. In the study by Swensen et al., 1049 patients had 2832 nodules (37,38). When multiple nodules that are few in number and of small size are present, each nodule is often treated as a solitary nodule, particularly in patients without a significant history of malignancy. A solitary pulmonary nodule can represent a granuloma, lung cancer, solitary pulmonary metastases, hamartoma, carcinoid, arteriovenous malformation (AVM), and intrapulmonary lymph node.

The presence of multiple nodules implies a slightly different differential diagnosis as opposed to the solitary or dominant pulmonary nodule. Causes of multiple nodules include infection such as septic emboli, fungal infection; pulmonary infarcts; metastatic disease; and inflammatory noninfectious lung disease such as vasculitis, lipoid pneumonia, cryptogenic organizing pneumonia (COP), and alveolar sarcoid. Etiologies of multiple nodules can lead a solitary or dominant pulmonary nodule in their early phase of lung involvement. A diffuse nodular pattern occurs when a very large number of small pulmonary nodules of similar size are present and is assessed best using high-resolution CT (HRCT) techniques.

The evaluation of pulmonary nodules includes detection, characterization, and subsequent management. PET/CT is primarily used for characterization of a solitary or dominant pulmonary nodule. The probability that a nodule represents malignancy relies on both the clinical scenario including patient risk factors for cancer and imaging characteristics, as assessed on both PET and CT. For

this reason, discussion will cover PET and CT findings that can be encountered during the workup of nodules including possible pitfalls and the role of PET/CT.

PET for Nodule Characterization

In FDG PET or PET/CT, qualitative (e.g., visual) and semiquantitative measures of FDG uptake are useful in assessing pulmonary nodules. Qualitative evaluation is performed by comparing the intensity of FDG uptake in a focal lung lesion with normal mediastinal activity. If the uptake appears visually higher than that of the normal mediastinum, malignancy is suspected. Semiquantitative determination of FDG activity is accomplished by calculating the SUV, or using the lesion to background ratio. The SUV represents the amount of uptake in a given region of interest (ROI) in relation to the average uptake throughout the body. It can be calculated from the following formula (39):

$$\text{SUV} = \frac{\text{Activity concentration (MBq/g)}}{\text{Injected dose (MBq)/Patient weight (g)}} \quad (1)$$

The maximum SUV that has been used by most investigators is 2.5 (39–41), although early on some authors used 4.0 (42,43). For most clinicians and imagers, a lesion with an SUV greater than 2.5 is suspicious for malignancy (Fig. 16). Duhaylongsod et al. prospectively evaluated 87 subjects with indeterminate focal abnormalities with PET/CT. Using a mean SUV of greater than or

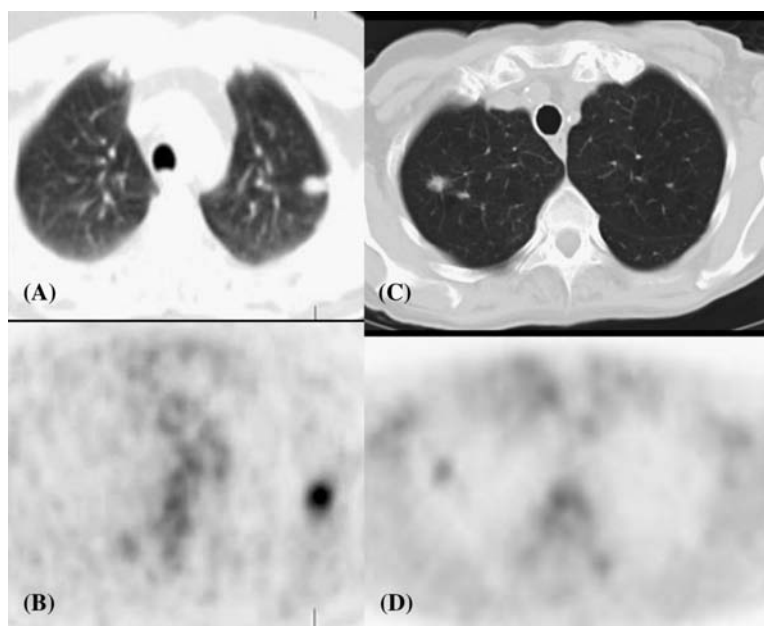


Figure 16 Left upper lobe pulmonary nodule discovered on a screening CT is evaluated by PET/CT. CT scan (A) shows the peripheral nodule measuring 8×10 mm. The corresponding transaxial FDG PET slice (B) shows the increased uptake (SUV 4.2). In another patient an 8-mm spiculated right upper lobe nodule on CT (C) has an SUV on FDG PET (D) of 2.9. At pathology both of these were adenocarcinomas.

Table 3 PET in Solitary Pulmonary Nodules

Author (reference)	<i>n</i>	Sensitivity ^d	Specificity ^d	Accuracy ^d
Patz et al., 1993 ^a (39)	51	89	100	92
Lowe et al., 1994 ^b (42)	88	97	89	—
Lowe et al., 1997 ^b (43)	197	96	77	89
Duhaylongsod et al., 1995 ^a (581)	87	97	82	92
Gould et al., 2001 (45)	1474 ^c	96.8	77.8	—

No correlation between lesion diameter and FDG uptake.

^a2.5 SUV cutoff.

^b4.0 SUV cutoff.

^cMeta-analysis.

^din percentage.

equal to 2.5, malignancy was detected with a sensitivity, specificity, and accuracy of 97%, 82%, and 92%, respectively (44) (Table 3).

A more recent meta-analysis by Gould et al. published in 2001 showed that FDG PET carries a mean sensitivity of 96.8% and specificity of 77.8% for identification of malignant pulmonary nodules and mass lesions (45). In this meta-analysis, no difference in accuracy between qualitative and semiquantitative (i.e., SUV) was found.

In spite of these high sensitivities, exceptions occur, some of which are predictable. Nodule size, the coexistence of inflammatory disease, and the histological type of the malignancy may all confound the evaluation of nodules using PET/CT.

False positives

Increased FDG uptake occurs in the setting of primary and secondary lung malignancy and also benign disease. False-positive FDG PET studies have been reported in infectious or inflammatory processes such as tuberculosis (46–49), *Mycobacterium avium-intracellulare* infection

(50,51), aspergillosis (52,53), sarcoidosis (53–56), vasculitis (57,58), acute lung infarction (59), and organizing pneumonia (60,61). Low levels of metabolic uptake on PET have been associated with hamartomas (62) and rounded atelectasis (59).

Investigators from several groups have tried to reduce potential false-positive PET results. Imaging lung nodules at two different time points during FDG uptake (i.e., dual-time-point imaging) has been used in the effort to increase specificity of FDG PET for discriminating benign from malignant nodules (Fig. 17). In a study by Zhuang et al. involving in vitro samples and animal and human subjects, malignant lesions showed a significant increase in 18F-FDG uptake (SUV), while benign inflammatory lesions showed a decrease over time (63). One possible reason for this difference is that while both inflammatory and cancerous lesions overexpress glucose transporters and hexokinase fostering increased uptake of FDG, malignant entities have on average lower glucose-6-phosphatase (G6Pase) activity than benign lesions. While the concomitant expression of G6Pase in benign disease permits the egress of the radiolabeled glucose from the cells, the

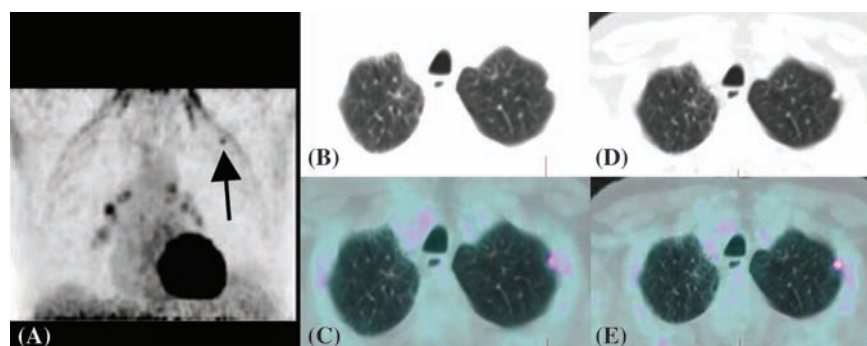


Figure 17 False-positive dual-time-point imaging. Bilateral hilar lymphadenopathy suggestive of sarcoidosis is seen on the anterior view of a maximum intensity projection from a PET/CT (A). The patient also had a metabolically active left upper lobe pulmonary nodule (arrow). The PET/CT performed with the routine one hour delay (B,C) showed uptake in the peripheral nodule, SUV 3.0. In an attempt to better characterize the nodule, a delayed PET/CT of the chest was performed (D,E) showing an increase in uptake to SUV 4.1. Because of concern for malignancy in this patient, biopsy was performed and revealed noncaseating granulomas.

relatively inadequate expression of this enzyme in malignant disease results in trapping of the radiolabeled glucose. Additional investigation by Matthies et al. has reached similar conclusions about dual-time-point imaging (64). Although these studies appear promising, the use of dual-time-point imaging remains controversial. In fact, not all malignant lesions exhibit increasing FDG uptake over time, and some benign lesions such as sarcoidosis can also demonstrate this behavior (65) (Fig. 17).

False negatives

False negatives are also predictable to some extent. Neoplasia can be mistaken as a nonneoplastic process, when the lesion is too small or of low metabolic activity, as with typical carcinoids and bronchioloalveolar carcinoma (BAC) (see below), or when there is a low density of tumor cells (66).

The size threshold for a pulmonary nodule below which PET is unreliable has not been clearly established. Identification of uptake depends on a number of factors including partial volume effects related to the limitation in

spatial resolution of the PET scanner, respiratory motion of the nodule, and, occasionally, the paucity of tumor cells within small abnormalities (66). The reported spatial resolution of the current generation of PET scanners in PET/CT units ranges from 4.5 to 6–7 mm according to the National Electrical Manufacturers Association standards (67); however, this value is measured under ideal conditions. The spatial resolution of the PET systems in current practice is less, typically between 5 and 10 mm (68), due to changes in sampling and filtering, scattered and random events, and respiratory motion. When SUV or even qualitative criteria are applied to smaller lesions, false-negative results may be caused by partial volume averaging effects (Fig. 18) (69).

To date, inconsistent and little information is available about PET performance for nodules less than 1 cm in size. Bastarrika et al. investigated the utility of PET in evaluating nodules of 5 to 10 mm in diameter and noted that the apparent uptake in nodules decreased when the diameter was less than twice the spatial resolution of the system (approximately 7–8 mm) (70). A phantom study with ^{18}F -FDG-filled spheres measuring between 6 and

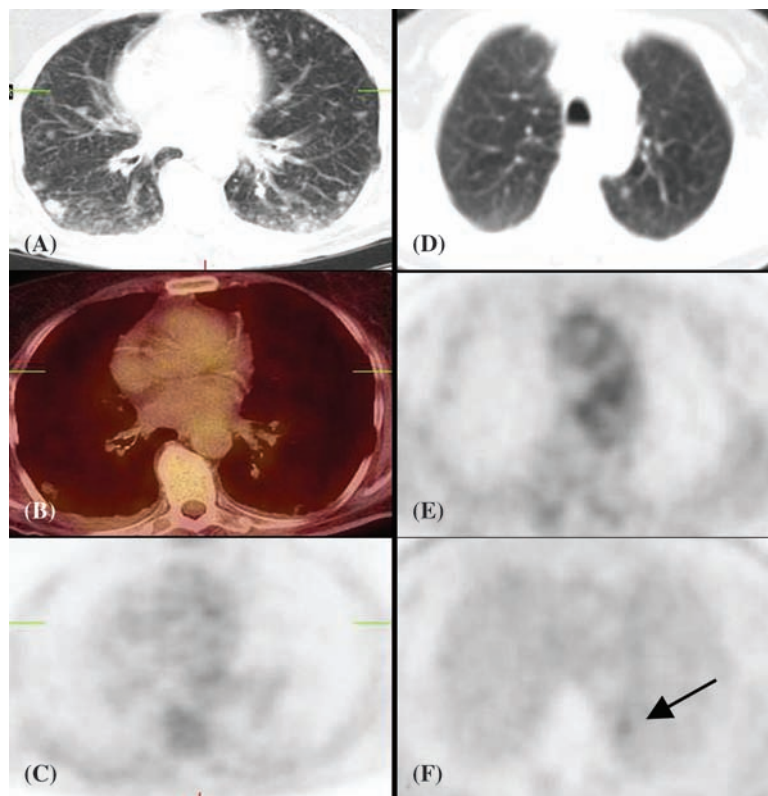


Figure 18 False-negative PET/CT studies in two different patients. The first patient (A–C) has multiple stable peripheral nodules and a newer slightly larger (7 mm) nodule in the right lower lobe on CT (A). A PET/CT was subsequently performed with the nodule negative on fused (B) and PET (C) images. Because of clinical suspicion for malignancy, the nodule was resected and was found to be an adenocarcinoma. In the second patient (D–F), the CT (D) shows a 6 mm nodule in the left posterior upper lobe, which on the attenuation-corrected PET images (E) was negative, but on the uncorrected image (F) activity is identified (arrow). This also proved to be an adenocarcinoma.

22 mm by Coleman et al. demonstrated that the detection of nodules of less than 7 mm was unreliable (71). A prospective study of 136 noncalcified nodules measuring less than 3 cm in diameter showed no FDG uptake in any of the 20 nodules less than 1 cm in diameter, regardless of histology (72). A study by Wiethoelter et al. in 2006 showed that pulmonary metastases of 8 to 10 mm in diameter could be accurately detected by means of 18F-FDG PET/CT with a sensitivity of 78.4%. The sensitivity of PET dropped to 40.5% for nodules 5–7 mm in diameter (73). However, in a smaller series of patients with nodules less than 1 cm in diameter, there was a high sensitivity and a high negative predictive value of 94% (74).

A possible approach to improving the detection and PET characterization of small lung nodules is the evaluation of nonattenuation-corrected images (Fig. 18). A higher target-to-background ratio, i.e., better visibility of lesions, was reported on non-attenuation-corrected PET images in two lung cancer studies (75,76) and in a phantom and patient study (77). However, other data suggest that attenuation-corrected and non-attenuation-corrected images appear to be comparable for lesion detection in the thorax and lungs (78). This has been supported by another recent study from Reinhardt et al., who suggested that reconstruction of non-attenuation-corrected PET images for FDG PET/CT imaging is not of particular value (73). In fact only 3.5% of PET-positive pulmonary metastases were seen on non-attenuation-corrected images but not on attenuation-corrected images. Nonetheless, 41.4% of pulmonary lesions in this series showed improved visibility on non-attenuation-corrected PET images, and even these authors concluded that attenuation-corrected PET images should be carefully scrutinized for foci of even slightly increased FDG uptake corresponding to pulmonary nodules detected on CT imaging. The differences in visibility were more pronounced for lesions smaller than 1 cm in diameter and in lesions located in the periphery and base of the lung.

Before defining a role of PET and/or PET/CT in the evaluation of small-sized nodules, further technological refinements and testing of acquisition protocols to overcome partial volume effects (i.e., respiratory gating) and mathematical corrections for small size need to occur (68). Therefore, in patients with a history of malignancy, small pulmonary nodules and metastases are still followed by CT to monitor for growth or response to therapy despite lack of FDG uptake.

In addition to small nodule size, two other major factors, hyperglycemia and low tumor metabolic activity, can lead to false-negative FDG PET studies. Hyperglycemia results in decreased FDG uptake in malignant lesions, as glucose competes with FDG for the glucose transporter (79,80). The inhibitory effect is most significant when the hyperglycemia is of rapid onset. Chron-

ically elevated glucose levels have been reported to reduce tumor FDG uptake to a lesser degree, on the order of 10% (81). To a large extent, hyperglycemia leading to decreased FDG uptake can be avoided by careful attention to patient preparation, e.g., appropriate fasting, any patient history of diabetes mellitus, and routine glucose monitoring at the PET/CT imaging facility prior to administration of FDG.

A critical concentration of metabolically active malignant cells is necessary to detect FDG uptake. In an *in vitro* study, FDG uptake was related to the number of viable cancer cells (82). In a study by Dewan et al., a 1-cm nodule identified as a scar adenocarcinoma was associated with a negative PET scan and was attributed to the relatively few malignant cells interspersed in a large amount of fibrous stroma (83). Malignancies with low metabolic activity such as BAC lung carcinoma or carcinoid also may have low uptake of FDG (84,85). Several reports have showed the relationship between glucose metabolism measured by FDG PET and the proliferative rate or malignancy grade in tumors. Okada et al. demonstrated that Ki-67 immunoreactivity, an indicator of cells' proliferative activity, increased in proportion to FDG uptake (86). Duhaylongsod et al. reported that high levels of glucose metabolism were associated with faster rates of tumor growth (41).

CT Characterization of Lung Nodules

The integration of CT and PET information has improved correlation of functional and morphologic characteristics (Table 4). Characterization of FDG-avid findings as inflammatory, such as focal mucoid impaction or bronchiolitis, is improved by assessing the findings on corresponding CT images. Increased specificity may be lent to a low-metabolic nodule by identifying the presence of CT characteristics of a benign entity, such as calcification in a granuloma (87). Additionally, the routine review of the CT scan images may yield other significant findings. For example, nodules that may be too small to assess for metabolic activity may prove clinically significant such as representing early metastases in a patient with known malignancy. Other important abnormalities such as an AVM are worth identification, although low in metabolic activity. A review of the CT characteristics that may be helpful for interpretation of nodules will ensue in this section. Many of the benign focal entities that may lead to focal nodular opacities will be briefly mentioned as part of differential diagnoses but discussed in greater detail later in the section pertaining to benign parenchymal disease. Note is made that the assessment of the lung parenchyma and small lesions may be limited by increased artifacts from respiratory motion if the CT portion of the PET/CT is obtained in quiet respiration.

Table 4 PET, CT, and CT Enhancement Characteristics in Focal Lung Disease

PET imaging	Entity	CT morphology/ associated structures	CT attenuation	CT nodule enhancement study
Increased metabolic activity	Lung cancer	Nodule or mass; spiculated, lobulated borders; round	Soft tissue; occasional calcifications; necrosis present in larger lesions	>10 HU incremental increase
Variable, may have low- metabolic activity	Bronchioloalveolar components in lung cancer	Poorly margined borders; conform to adjacent structures; air-bronchograms if solid component	Entirely or part ground-glass attenuation	Technique is not applicable
Increased metabolic activity	Metastases (solitary or multiple)	Well circumscribed, irregular borders; round, lobulated; may have halo of ground glass (hemorrhage)	Variable depending upon primary; may be predominantly calcified (osseous, thyroid), fat (liposarcoma)	More commonly >10 HU incremental increase
Variable, may have low- metabolic activity	Carcinoid	Well-circumscribed margins; round; can be centered in airway	Soft tissue	Enhance avidly
Variable	Mucoid impaction	Tubular, oblong in shape; bronchus, if visible, comes to abrupt termination	Variable from low attenuation to calcified	Central area fails to enhance
Low metabolic activity	Hamartoma	Well-circumscribed, lobulated borders	Popcorn calcifications; fat attenuation	<10 HU incremental increase
Variable	Infarct	Wedge-shaped peripheral focal density abutting the pleura; sharp or poorly defined borders related to hemorrhage	Soft tissue and ground glass	Typically not assessed with this method
Low Low	Scarring Rounded atelectasis	Oblong Round mass like density; diffuse pleural thickening with possible chronic effusions; “Comet-tail sign” Volume loss	Soft tissue Soft tissue	Fail to enhance May enhance like normal lung
No metabolic activity	Arteriovenous malformation	Enlarged feeding artery and draining vein	Soft-tissue attenuation on noncontrast CT; intense enhancement during arterial phase on contrast CT	Not assessed using this technique
No activity	Intrapulmonary lymph node	Small, located in subpleural region; well circumscribed; round or ovoid; <2.0 cm	Soft tissue attenuation	Often too small to be characterized with method

Attenuation

Initial assessment of a nodule on CT includes evaluating attenuation. When assessing the attenuation on thick sections, partial volume averaging and image misregistration may affect the apparent attenuation. For example, a

solid nodule on thin sections can appear ground glass in attenuation on thick sections. On attenuation corrected images acquired in quiet inspiration, partial volume averaging, and misregistration are factors that can affect CT attenuation measures, just as they affect SUV measurement. Assessment of attenuation may not be possible

unless these artifacts are felt not to be present. Additionally, decreased radiation exposure, such as CT scans obtained with reduced dose technique such as that commonly used in PET/CT for attenuation correction, leads to increased image noise and apparent areas of low attenuation. Therefore, a diagnostic CT may be warranted to assess attenuation characteristics if there is concern about reliability of the measurements and if the presence or absence of specific attenuation characteristics might lead to a change in management.

Ground-glass attenuation

A nodule containing ground-glass attenuation has been termed “subsolid.” Ground-glass attenuation is an increase in lung density that is less than soft tissue attenuation, such as the attenuation of the adjacent vessels. Ground-glass attenuation can be frequently detected on low-dose CT technique utilized for attenuation correction. A subsolid nodule may be “pure ground-glass” in attenuation or “part-solid,” meaning denser solid attenuation components are present in addition to ground-glass density (Fig. 19). While pure ground-glass nodular densities may prove inflammatory, these nodules have been associated with premalignant and malignant forms of adenocarcinoma, termed atypical adenomatous hyperplasia (AAH) and BAC, respectively (88–92). A nodule with low-metabolic activity of this morphologic appearance may well still represent a BAC or premalignant forms.

In the Early Lung Cancer Action Project, of 44 cases of subsolid nodules, malignancy was diagnosed in 15 (34%) as opposed to a 7% for solid nodules, with part-solid nodules having a malignancy rate of 63% while nonsolid

nodules had a rate of 18% (93). If malignant, pure ground-glass nodules have been associated with very long doubling times on the order of 813 days (94) and 880 (95). Part-solid nodules raise suspect for adenocarcinoma with invasion and managed more aggressively (Fig. 20) (95,96). The more aggressive behavior of adenocarcinomas with part-solid components has been reported to have shorter doubling times on the order of 457 days, while solid adenocarcinomas have doubling times of 149 days (94). Since doubling times relate to proliferative rates in these nodules, FDG uptake is expected to relate to these doubling times (82,97). Consequently, while many BACs may be PET negative, their uptake increases with their aggressiveness (Fig. 20) (84,97).

A ground-glass attenuation halo around the periphery of a nodule has been correlated with hemorrhage and has been described in inflammatory processes such as fungal infections, septic emboli, vasculitis, and metastatic disease (98). (Fig. 21) These processes tend to manifest as multiple nodules although can present as a solitary lesion. A reverse halo, in which soft tissue attenuation surrounds a ground-glass central region, has been described with COP (Fig. 21).

Calcifications and fat attenuation

Calcifications can occur in benign and malignant nodules. Certain patterns of calcification have been described in benign entities. “Popcorn” appearing calcifications have been associated with hamartomas (99). These nodules typically measure 2.5 cm or less, have a smooth edge, and contain focal collections of fat or fat alternating with areas of calcification (99). In a study by Siegelman et al.,

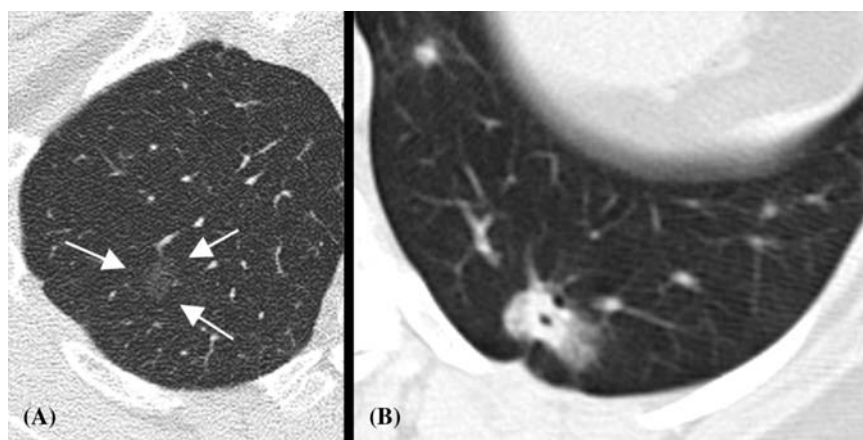


Figure 19 Subsolid nodules (A) Pure ground-glass nodule. The nodular density is mildly increased in attenuation in comparison with surrounding parenchyma yet without soft tissue density that would be of attenuation similar to that of the vessels. (B) Part solid nodule. Adenocarcinoma with BAC features has solid attenuation areas with a small lucency within representing an area of pseudocavitation in addition to ground-glass opacities along the left aspect of the nodule. A bronchus is located in the periphery of the nodule also. *Abbreviation:* BAC, bronchioloalveolar carcinoma.

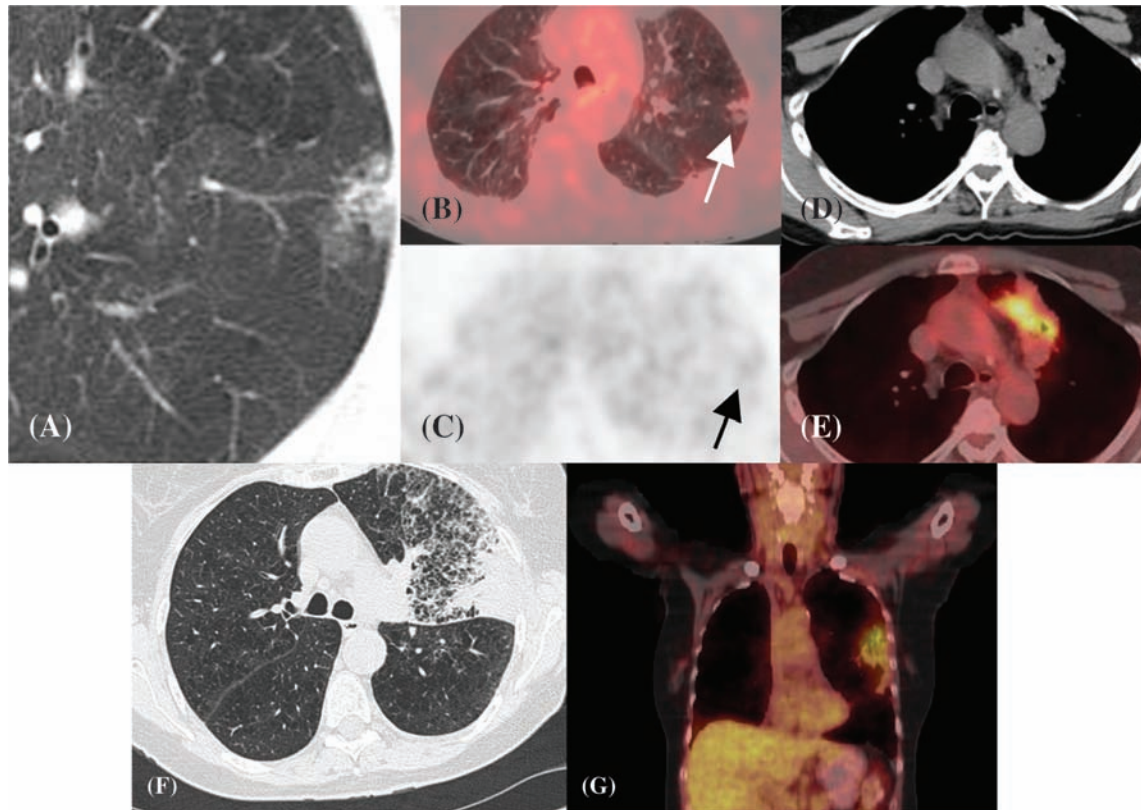


Figure 20 (A–C) Left upper lobe semisolid nodule on CT (A) was found to be BAC. Corresponding PET fused (B) and unattenuated PET images (C) show minimal uptake in the lesion (arrows) that is well below the threshold for malignancy, a frequent finding in BAC. Another patient (D–E) has a more solid, aggressive left upper lobe lesion on CT (D) that had shown rapid growth. On PET (E), this lesion showed a maximum SUV of 4.6 and proved to be mixed BAC with an adenocarcinoma component. (F–G) Pneumonic BAC in another patient. Note the triangular consolidation and ground-glass opacity adjacent (E) with and increased uptake on coronal fused PET/CT (F). While this can easily represent pneumonia, the patient lacked symptoms that would be expected with pneumonia. Mildly nodular ground-glass opacity is also present in the left lower lobe, consistent with multifocal tumor. *Abbreviation:* BAC, bronchioloalveolar carcinoma.

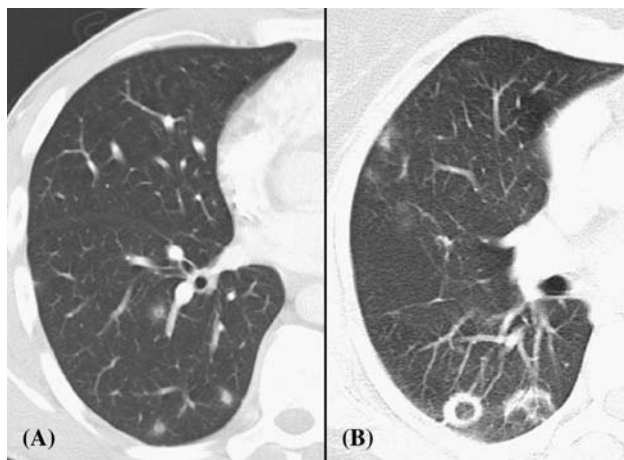


Figure 21 Ground-glass multiple nodules. (A) Invasive bronchopulmonary aspergillosis. Multiple solid nodules are present with poorly defined halos of ground-glass attenuation representing hemorrhage in this form of infection. (B) Reverse halo sign described with cryptogenic organizing pneumonia. Note the soft tissue density surrounding central ground-glass attenuation areas in the nodules.

28 of 31 proven or 16 presumed hamartomas satisfied these criteria (Fig. 22).

A nodule when homogeneously calcified is highly suggestive of prior granulomatous exposure. Additionally, calcifications in a lamellar pattern with multiple concentric rings and central calcifications are associated with granulomatous disease. However, a nodule with centrally located calcifications in the presence of a dominant soft tissue component cannot be determined to be benign, and follow-up or other investigation may be warranted. Clinical history is important when assessing nodules with benign-appearing calcification patterns. Ossifying and calcifying sarcomas present as a small nodule or nodules in the lungs with varying degrees of soft tissue and calcification. Homogeneously calcified nodules in the appropriate clinical scenario may represent metastases from osteogenic tumors in addition to those from thyroid carcinoma (Fig. 22).

Speckled calcifications are suspicious for malignancy and correlate with dystrophic calcifications in necrotic areas of tumor on pathology (100). Additionally, an eccentric solitary calcification within a nodule cannot be

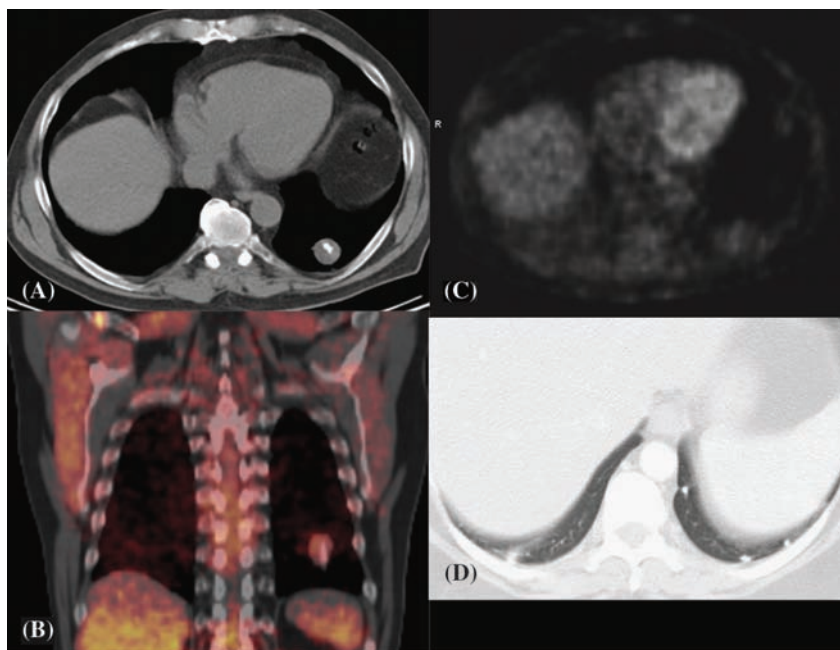


Figure 22 Calcified nodules. (A–C) Hamartoma containing calcifications. (A) On CT, popcorn pattern of calcifications with mild low attenuation areas possibly representing fat. A confirmatory PET/CT study demonstrates a lack of metabolic activity on coronal PET/CT (B), attenuation corrected (C) PET image. (D) Axial CT section viewed under lung window settings of a patient with history of metastatic osteosarcoma. Multiple small calcified nodular densities are predominantly at the lung bases, which would be consistent with a hematogenous distribution. These calcified nodular densities can be misinterpreted as granulomatous exposure without clinical history of an ossifying or calcifying primary.

used to characterize a nodule as benign, as a calcified granuloma or calcification within a bronchus may have been engulfed by an adjacent malignancy (100).

In addition to the hamartoma, focal exogenous lipid pneumonia from ingestion of oily materials, typically mineral oil laxatives, can lead to areas measuring the density of fat associated with varying degrees of soft tissue (Fig. 23). Fatty nodules and masses, however, are

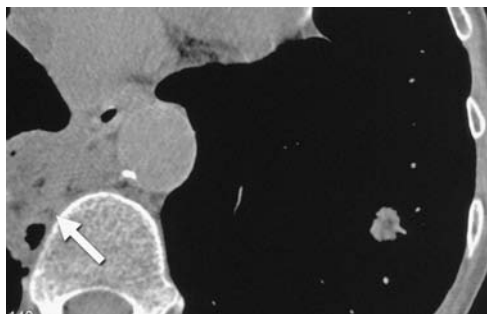


Figure 23 Exogenous lipid pneumonia. An elderly female demonstrating a spiculated nodule, which on 1.5-mm soft tissue section low attenuation consistent with macroscopic fat is identified in the nodule (arrow) and mass-like areas in the right lower lobe, confirming the diagnosis of lipid pneumonia.

suspicious for metastatic disease in the clinical scenario of a primary liposarcoma.

Morphology

Borders

Morphology assessment includes the evaluation of a nodule's margins and internal architecture. Spiculated borders have been associated classically with primary malignancy and represent desmoplastic response (100–102). Pleural tags are linear fibrotic bands emanating from a nodule and are associated with pleural retraction. Pleural tags have been associated with both benign disease and primary lung malignancies (Fig. 24). In a study by Zwirer et al., pleural tags were identified in three benign nodules (27%) and 49 malignant lesions (58%) (100). Lobulation has been described with malignancy and benign entities such as hamartomas or granulomas (100,102). While often benign, a smooth, round nodule in the lung parenchyma may prove to be a primary or secondary malignancy (102). Geometric nodular densities have a lower probability for malignancy, as in a study by Takashima, polygonal shape and a nodular density with a ratio of a maximal transverse dimension to maximal longitudinal dimension of greater than 1.78 were associated with very high specificity for benignity (103).

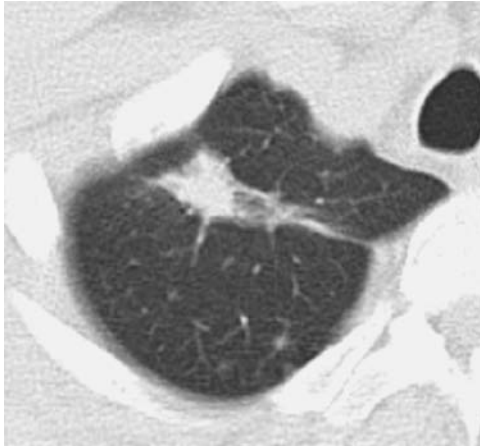


Figure 24 Spiculated nodule with pleural tag. Axial CT section demonstrates a pleural tag emanating from a large nodular density in the right upper lobe. The spiculated margins and size are highly suspicious for a primary lung neoplasm.

Clustering of nodules

The clustering of small equal-sized nodules has been described with bronchiolar disease. The nodular densities are centrilobular in distribution, involving the bronchiolar regions of the secondary pulmonary nodule. Classically, but not always, branch-like opacities are also evident leading to clustered nodules, representing inflammation and infection in terminal respiratory bronchioles, giving rise to the appearance of a tree budding in spring, termed a “tree-in-bud” pattern (Fig. 25) (104,105). The tree-in-bud

pattern has been associated with infection from bacterial, fungal, and viral etiologies. Focal lung disease in a branching morphology is suggestive of mucoid impaction rather than a nodule.

Internal architecture

Internal morphology and texture can be assessed on CT. More commonly, nodules contain soft-tissue density without any air containing structures. While air bronchograms are commonly seen in pneumonia, air bronchograms can be identified sometimes in a solid or subsolid nodule (Figs. 19 and 20). The term “pseudocavitation” is typically used when a small bubble-like lucency is present. The lucency represents spared alveoli or terminal bronchioli. Air-bronchograms and pseudocavitation in a chronic nonfluctuating nodule or mass raise suspicion for BAC and adenocarcinoma in which “lepidic” growth, defined as growth around rather than invasion of the alveolar wall, lead to spared air-containing areas (100,106).

True cavitation within a nodule has been associated with squamous cell carcinomas and focal lung infection, including atypical mycobacteria and invasive aspergillosis. When multiple, fungal infection, septic emboli, vasculitis, and rheumatoid nodules are a consideration. Cavitation of a nodule or mass in an “air-crescent” configuration, in which curvilinear lucency is interposed between the nodule periphery and a central rounded soft tissue region, has been associated primarily with angioinvasive *Aspergillus* infection that affects severely neutropenic individuals (98). A similar appearance, however,

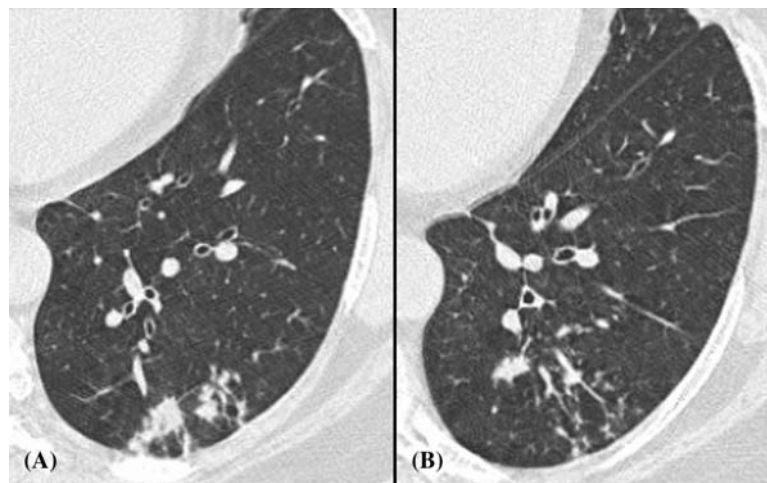


Figure 25 Inflammatory nodules. Multiple clustered nodules are identified in the left lower lobe. A more focal area of opacity in the left lower lobe (A) has smaller adjacent nodular densities. Additionally, a cluster of small nodules is identified. These nodular densities are in a tree-in-bud configuration, which are suggestive of an infectious process at the bronchiolar level. Adjacent CT section (B) also demonstrates tree-in-bud nodules. This patient had *Mycobacterium avium-intracellulare* complex infection. The larger nodule in the left lower lobe has a higher likelihood of being inflammatory given other smaller nodules in the tree-in-bud pattern. This nodule was shown to resolve along with others on follow-up CT.

can be seen with saprophytic fungal infection of a preexisting cavity from tuberculosis, bronchiectasis, emphysema, or other cystic lung disease.

Associated structures

Associated structures such as vasculature and bronchi assist in characterizing lung nodules. Scrutiny of relationship of a bronchus to a nodule has also been facilitated by high resolution, thin section imaging, and multidetector CT. An abrupt cutoff of a bronchus within the nodule, penetration of a bronchus with tapered narrowing and obstruction in a nodule, and an intact patent bronchus passing around the periphery of the nodule was more frequently seen in malignant than benign nodules. A bronchus displaced and compressed by a nodule was more commonly present in benign entities. In malignant nodules, rarely was the bronchus displaced or compressed by the nodule (1.9%), while no benign lesions had a bronchus that penetrated into the nodule with tapered narrowing and obstruction. Small nodular densities that are identified in small dilated peripheral bronchi, which are typically larger than the accompanying pulmonary arterial branch, are suggestive, but not diagnostic, of focal areas of mucoid impaction.*

The presence of a feeding vessel may well represent hematogenous processes such as metastases and vasculitis; however, this finding has proven less specific in terms of the diagnosis (107). Additionally, apparent entry of a vessel into the center of nodule may be created by partial volume averaging on sections on the order of 5 to 7 mm. In nine patients with confirmed septic emboli, Dodd et al. reported that 52 (37%) nodules and 11 (22%) wedge-shaped opacities had feeding vessels; however, scrutiny of the multiplanar reconstructions (MPRs) and maximum intensity projections (MIPs) revealed that the vessels passed around rather than directly entered the nodule (108). Intracavitary debris may be present representing necrotic lung in an infarct.

When a nodule is associated with a dilated, directly associated feeding pulmonary artery, considerations include pulmonary infarction, supplied by a thrombosed feeding vessel, or an AVM fed by a single or multiple enlarged feeding arteries. An enlarged vein or veins drain blood from the AVM (Fig. 26). AVMs are direct communications of the pulmonary arterial and venous systems, and thereby blood bypasses the capillary level. In these scenarios, a CT study with intravenous contrast may be warranted. Multiple AVMs occur in patients with multiple hereditary hemorrhagic telangiectasias, also termed Osler-Weber-Rendu disease. Pulmonary infarcts and septic emboli tend to be peripheral in location, given that pul-



Figure 26 Arteriovenous malformation. An arteriovenous malformation in the lingula has a nodular component. A prominent vessel representing a draining vein drains the nodular aneurysmal segment. Hypertrophied arterial supply to the aneurysmal segment is also present.

monary emboli and small organisms lodge in distal small vessels and tend to be multiple. A basilar predisposition is consistent with their hematogenous origin.

Size of Nodules

The probability that a nodule represents malignancy increases with increasing nodule size (109). As revealed through screening CT studies, small nodules on the order of 7 mm or less have a lower likelihood of malignancy. In particular, nodules that measure 4 mm or smaller have a less than 1% chance of representing malignancy, even in high-risk smokers. The possibility of malignancy for an 8-mm nodule is approximately 10% to 20% in high-risk patients without previous history of cancer (38,109,110). For nodules greater than this size, understandably the possibility of malignancy is higher.

Integrating PET Imaging, CT Findings, and Clinical Factors

CT provides additional and frequently invaluable information for interpreting the PET imaging results on PET/CT (Tables 4 and 5). Low FDG uptake nodule in combination with calcifications in a benign “popcorn” pattern and demonstrable fat on CT are very suggestive of a hamartoma. However, in the scenario of low-FDG uptake in a nodule, careful scrutiny of its CT appearance is essential. A nodule containing air-bronchograms, pseudocavitation, or ground-glass components cannot be deemed

*Qiang JW, Zhou KR, Lu G, Wang Q, Ye XG, Xu ST, Tan LJ. Clin Radiol 2004; 59:1121–1127.

Table 5 PET and CT Findings in Multifocal Nodular Lung Disease

PET imaging	Entity	CT morphology/associated structures	CT attenuation
Increased	Infectious bronchiolitis	Clustered small nodules, some in a branching tree-in-bud configuration; solitary or multifocal	Soft tissue
Variable uptake	Rheumatoid nodules	Well circumscribed, sharply defined borders; can have cavitation, thin wall; peripheral predisposition; variable size (3–30 mm)	Soft tissue
Increased	Wegeners	Nodules, masses, mass-like consolidation; poorly defined borders; cavitation not infrequent	Soft tissue
Increased	Septic emboli	Nodules, masses, peripheral in location; ground-glass periphery in early phase, with areas of cavitation in the later stages; borders can be well circumscribed; nodules in different phases of cavitation	Soft tissue
Increased	Lipoid pneumonia	Nodules, masses, mass-like consolidation with poorly defined borders; consolidation	Fat and/or soft tissue
Increased	Angioinvasive aspergillosis	Nodules, masses; confluent consolidation; ground-glass halo early in infection; cavitation in air-crescent pattern once neutropenia resolves; cavitates at the same time	Soft tissue
Increased	Metastatic disease	Well circumscribed typically; lobulated, round; halo of ground-glass when hemorrhagic	Soft tissue typically; Calcified—fine calcifications with gastrointestinal, genitourinary tumors; can be dense with thyroid, osseous primaries; fat—Liposarcoma
Increased	Cryptogenic organizing pneumonia (bronchiolitis obliterans organizing pneumonia)	Nodules, mass-like consolidation; Reverse halo sign (more solid rim, ground-glass centrally)	Soft tissue with ground-glass areas
Increased	Sarcoidosis “Alveolar form”	Nodules and masses; air bronchograms can be present; Can lack the diffuse perilymphatic nodular pattern typically associated with sarcoidosis; accompanied by symmetrical adenopathy	Soft tissue
Variable, may have low metabolic activity	Multifocal bronchioloalveolar/adenocarcinoma of the lung	Masses/consolidation with poorly marginated borders; conform to adjacent structures; air-bronchograms or pseudocavitation if solid component; multiple centrilobular ground-glass nodules; associated with areas of diffuse consolidation in pneumonic form	Pure ground-glass attenuation or part-solid/part ground-glass attenuation

benign, as BAC and low-grade adenocarcinomas remain a consideration. Nodules that are endobronchial involving the trachea, mainstem, lobar, and even segmental airways with low uptake additionally should not be assumed to be benign, as carcinoid tumors have been associated with a variety of metabolic uptakes. Nodules of small size may lead to false-negative assessment of FDG uptake. In distinction, the pattern of highly suspicious morphologic

factors, large size, and increased uptake in a solitary or dominant lesion raises suspicion for malignancy.

Bayesian analysis

The clinical scenario affects the likelihood that a nodule is malignant. A number of CT variables have been shown to predict an increased probability for malignancy (Table 6).

Table 6 Probability of Malignancy According to Clinical and Radiographic Findings

	Characteristic	Benign	Malignant
Clinical (586)	Gender (111)	NC	NC
	Age	<60 years	>60 years
	Prior smoking	No	Yes
	Current smoker	No	Yes
	Prior malignancy	No	Yes
CT (111)	Shape	Linear	Round
	Size	<1.5 cm	>2 cm
	Lobulation	None	>3 concavities
	Border definition	Poorly defined	Well defined
	Spiculations	None	Involving entire margin
	Pleural indentations	None	>2
	Attenuation homogeneity	Homogeneous	Heterogeneous
	Satellite lesions	None	>6
	SUV (39, 41–45, 588)	<2.5	>2.5
PET (587)	Pleural effusion	None	>1/3 thoracic cavity
	Lymphadenopathy (588)	None	Metabolically active lymph node
	Extrathoracic malignancy (587)	None	>1 extrathoracic active sites

Abbreviation: NC, noncontributory. Source: From Refs. 38,582–585.

Clinical factors such as smoking history, environmental exposure, family history, patient age, and previous history of malignancy have been shown to affect significantly the likelihood of malignancy. As an example, Swensen et al. utilized Bayesian analysis to study the influence of clinical factors on probability of malignancy. They reported that a nonspiculated 1-cm nodule in a nonupper lobe location on chest radiograph in a 35-year-old without history of cigarette use or other cancer had a 0.02 chance of malignancy as compared with the 0.79 likelihood of malignancy of a 1 cm spiculated nodule in the upper lobe of a 75-year-old patient with a previous history of cancer and smoking (101). The addition of PET information to CT has also been reported, as the combination of PET, CT, and clinical factors enabled a computer-aided diagnosis scheme to differentiate benign and malignant nodules better than either PET with clinical factors or clinical factors with CT in a study by Nie et al. (111). The influence of many imaging factors that positively correlate with malignancy or, alternatively, decrease the possibility of malignancy are still not fully investigated at this point. For example, the likelihood that a 7-mm nodule in the setting of significant bronchiectasis, multiple nodules of similar size that have been shown to wax and wane, and airway inflammation is decreased relative to a similar nodule in an individual with no other lung pathology.

Incidental nodules upon PET/CT review

Thoracic PET/CT is typically performed to assess for already known worrisome focal lesions or to stage an already diagnosed cancer. Nonetheless, incidental media-

stinal and lung pathology that lacks or has only mild FDG activity is incidentally detected on CT images. Despite their low metabolic activity, these lesions may prove clinically significant, such as small metastatic lesions and vascular lesions including AVMs and aneurysms.

The detection of nodules on CT remains problematic. In reader studies pertaining to nodule detection, sensitivities for detecting nodules on CT scan range on the order of 51% to 80% (14,112–114). Knowledge of the nodule characteristics and scenarios in which nodules are overlooked is helpful for minimizing reader error. Central nodules that are located adjacent to vascular structures and bronchi are particularly difficult to detect (113). Additionally, faint ground-glass nodules may prove difficult to perceive on routine CT sections (115). In addition, the identification of nodules on CT attenuation correction sections obtained during respiration has been shown to have a sensitivity of only 37% (CI 24–51%) and a specificity of 79% (CI 66–89%) (116). This underscores the need, if clinical management would be affected, for a diagnostic quality CT scan to thoroughly assess for pulmonary metastases in patients with known malignancy.

Image workstations and picture archiving and communication systems facilitate cine viewing of CT studies, aiding in the identification of small pulmonary nodules. MIPS (113) that are reconstructed from thin section CT data have been shown to improve detection of nodules. Lastly, the development of computer-aided diagnosis has been shown to improve nodule diagnosis on diagnostic and screening CT but has not been investigated in the scenario of PET/CT (14,117–119).

Evaluation of pulmonary nodules, including PET/CT

The management of patients with a detected solitary nodule depends upon a number of factors such as the nodule's likelihood of malignancy and location and the patient's clinical status. Lesions, depending upon factors pertaining to the patient and depending on the likelihood of malignancy, are typically either assessed by imaging (PET, nodule enhancement, and/or follow-up by CT), sampled for cytology or histopathology, or immediately resected. A large amount of clinical expertise is required for addressing and managing patients with a pulmonary nodule, and a single algorithm does not apply to all cases. The management approach undertaken is also influenced by the expertise available in interventional radiology, cytopathology, bronchoscopy, and surgery.

For nodules on chest radiography, if confirmation of stability in comparison with prior radiographs cannot be made, CT imaging is typically performed to confirm the presence of a nodule and also characterize these lesions. Intravenous contrast is beneficial for assessing lesions that are large and, therefore, with a higher likelihood of representing malignancy. Additionally, intravenous contrast delineates mediastinal and hilar adenopathy from adjacent structures and can be utilized when chest radiographs demonstrate a lesion accompanied by adenopathy or a lesion with potential involvement of the mediastinum and hila.

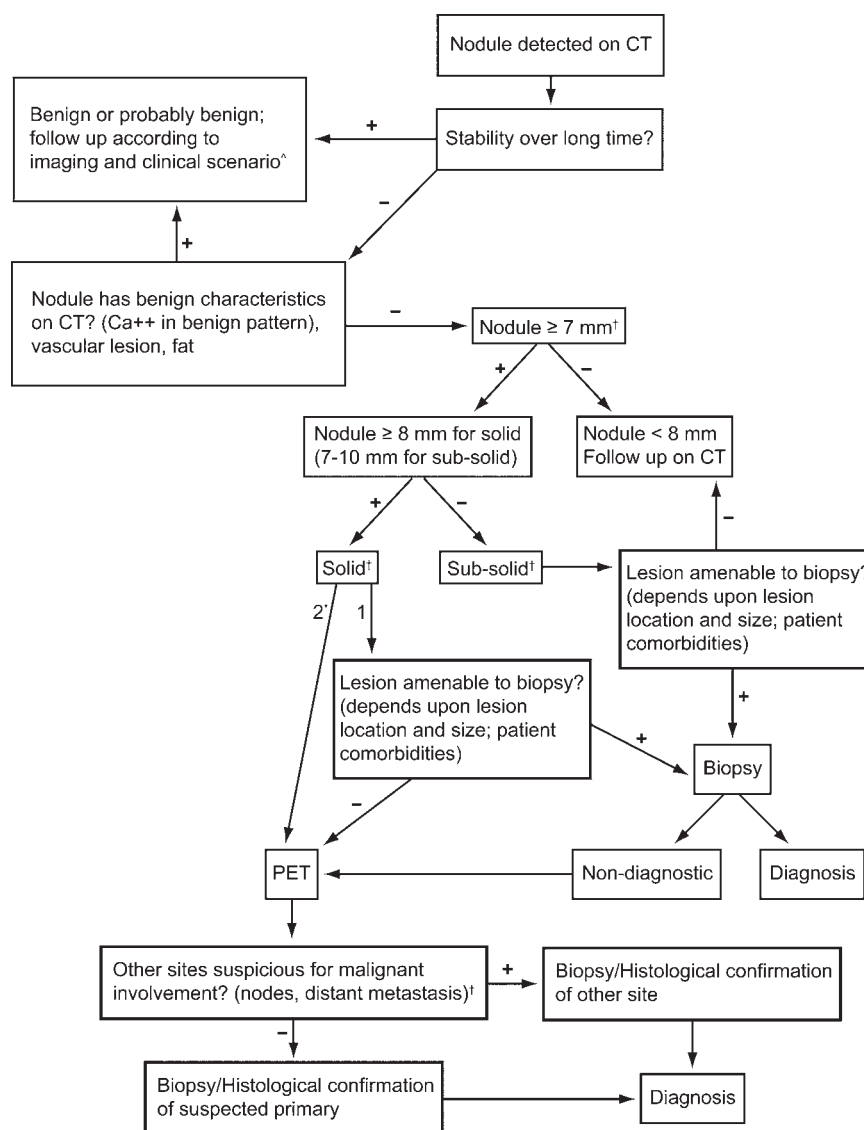
If the patient has had prior CTs, comparison to any previous studies to confirm stability is useful. Solid nodular densities determined to be stable for two years are more likely to be benign or less aggressive and can be observed. Tumors, however, such as carcinoid and other metastases may prove slow growing. Additionally, subsolid nodules representing BAC, predominantly those of pure ground-glass attenuation, have been associated with extremely slow growth. Thereby, a two-year stability does not exclude malignancy (120). In this scenario, yearly CT assessment may be warranted, potentially with low- or reduced-dose technique. A nodule determined to contain calcifications in a pattern associated with benign lesions, or demonstrable fat is suggestive of a benign entity, as described earlier. Otherwise, nodules are considered indeterminate.

Nodules that are 8 mm or larger, as compared with their smaller counterparts, have a greater likelihood of representing malignancy. These nodules are a size that can be further characterized using noninvasive or invasive methods (Fig. 27). Invasive methods include transthoracic needle aspiration and biopsy (TTNAB) and transbronchial sampling techniques. Lesions can also be biopsied using video-thorascopic assistance, a minimally invasive surgical technique. Needle aspiration with or without biopsy is typically performed on those nodules of high likelihood of malignancy based on combined clinical and nodule

factors. Percutaneous TTNAB can be used for sampling of more peripheral nodules, while a bronchoscopic approach may yield diagnostic samples for central abnormalities and some peripheral lesions directly along the course of bronchi. Nodules adjacent to the diaphragm, fissure, and against vascular structures may not be easily accessed by these methods, and the patient comorbidities influence the ability to perform these procedures. In this case, i.e., if a lesion is felt to be suspicious enough to warrant surgical biopsy, noninvasive assessment by PET/CT can be used to assess and stage individuals prior to any surgical intervention.

In the scenario in which the morphology of a nodule and patient characteristics may not indicate a high suspicion for malignancy, PET/CT can provide additional information by confirming a lack of significant nodule, lymph node, or extrathoracic FDG uptake. PET therefore may provide additional information that affects likelihood of malignancy and subsequent management. CT nodule enhancement is a technique that is less expensive and more available and therefore is a reasonable alternative when PET/CT is not available. One technique used for CT nodule enhancement has been assessed in a multicenter trial and entails the acquisition of thin sections on the order of at least 3 mm through a nodule prior to and after the administration of 100 cc of intravenous contrast injected at a rate of 2 cc/sec (121) (Fig. 28). Multiple postcontrast scans through the nodule are obtained at 1, 2, 3, and 4 minutes with reconstruction of data using a soft-tissue algorithm. For all timepoints, a ROI is placed on the image in which the nodule appears largest, using a soft-tissue window setting. An increase in attenuation of less than 15 HU is suggestive of benignity and of greater than 20 HU suggestive of malignancy. The sensitivity for malignancy is 98% and specificity for benignity is 58% (121). The low specificity of this technique is typically due to the enhancement of benign infectious lesions by greater than 15 HU. The use of a 10 HU threshold can also minimize false-negative results (121). Other techniques for nodule enhancement entail faster contrast injection rates. Also, some authors have suggested evaluating wash-out at 15 minutes after injection. A washout of 5 to 31 HU is also considered indicative of malignancy (122).

Research has not been directed toward comparing PET/CT and CT nodule enhancement to a great degree so far. At this time, PET/CT has been reported to perform better in characterization than CT nodule enhancement. In a study by Yi et al., PET/CT was shown to be more sensitive (96% vs. 81%; $P < 0.05$) and accurate (93% vs. 85%; $P = 0.011$) in a series of 119 patients (122). In this study, the specificity of CT nodule enhancement was higher than for PET, 93% versus 88%, respectively, although not statistically significant. The authors concluded that while PET/CT performed better, CT nodule enhancement had an



[^]Subsolid nodules may have very slow growth and thereby follow up for longer than 2 years may be warranted

[†]The clinical management path depends on the clinical suspicion related to PET and CT findings along with assessment of patient comorbidities and available biopsy techniques

^{*}PET may be performed prior to biopsy particularly when
1) lesions have very high likelihood of cancer:
large tumor size or presence of nodes, distant metastases on CT
2) High suspicion of benign lesion (i.e. hamartoma)

Figure 27 Algorithm for evaluation of a solitary pulmonary nodule using CT and PET/CT.

acceptable sensitivity and accuracy for malignant nodule detection and was a reasonable alternative when PET/CT is unavailable. In a study by Christenson et al. on 42 nodules, 25 malignant and 12 benign, PET had a higher specificity (76%) than CT nodule enhancement (29%), although slightly less sensitivity for PET (96%) than CT nodule enhancement (100%) (123). The discrepancy in the

reason why PET performed better than CT nodule enhancement is possibly related to differences in nodule enhancement technique between the two studies; however, data at this point is supportive of PET/CT being preferred to CT nodule enhancement. Nodule enhancement techniques, however, may prove complementary in the case of a suspected carcinoid in which a nodule with low metabolic

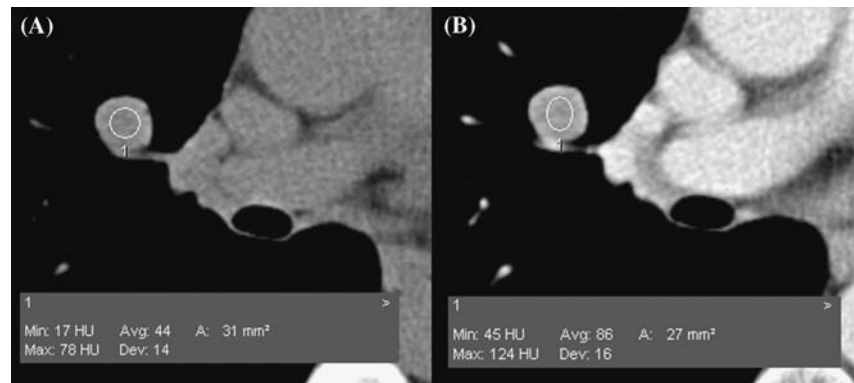


Figure 28 Nodule enhancement study. A well-circumscribed nodule in the right upper lobe demonstrates 44 HU prior to contrast administration (A). After the intravenous contrast injection, the nodule enhanced to 88 HU (B) at four minutes. The nodule was shown to be a carcinoma on pathology.

activity is shown to demonstrate intense contrast enhancement (124,125). Furthermore, follow-up CT imaging of nodules assessed as benign by PET/CT or nodule enhancement is warranted to exclude false-negative evaluations for malignancy.

Nodules measuring less than 8 mm are dilemmas, as they are often too small for invasive and noninvasive assessment. To maximize the ability to detect small changes in size, direct comparison with the most remote CT comparison is valuable for subsolid nodules in particular, as these nodules have been associated with very long doubling times (94,95). Additionally, stability for two years does not necessarily indicate benignity, particularly for subsolid nodules (91,94). Doubling times for cancers of pure ground-glass, part-solid, and solid attenuation have been reported to be on the order of 813 days, 457 days, and 149 days (94). For this reason, slow growth may be difficult to discern, particularly when interval follow-up is relatively small (Fig. 29). Additionally, for pure ground-glass opacities that have proven to be malignancies, decrease in size can occur by six months and even

after follow up of more than a year (91). Lastly, in addition to interval growth, the development of solid components should raise suspicion for development of invasive features (126). Some benign nodules may demonstrate slow growth, such as hamartomas. In a radiographic evaluation by Hansen et al., hamartomas were reported to increase by 3.2 ± 2.6 mm in 89 individuals (127). Individuals with a history of malignancy should be typically managed with knowledge of the tumor grade, type, and stage of their known malignancy (128).

Borderline or Slow-Growing Neoplasms

Atypical Adenomatous Hyperplasia

AAH is considered currently a preneoplastic lesion and has been integrated into the World Health Organization (WHO) classification (Table 7). AAH is felt to be a precursor to BAC. Such lesions are increasingly identified related to improvements in CT technology and image quality (89,129). AAH is a localized proliferation of

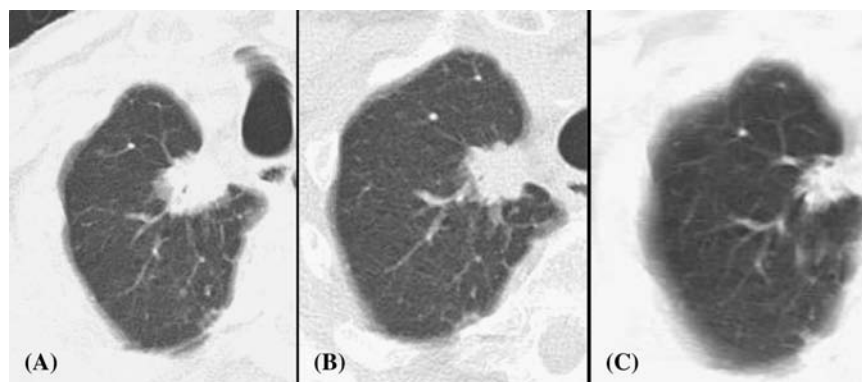


Figure 29 Benefits of comparison with more remote previous comparison studies so that slow growth can be identified better on. Current study (A) in comparison with CT performed seven months prior (B), a large nodule appears stable; however, in comparison with two years prior (C), the lesion is more readily identified to have increased in size.

Table 7 2004 WHO Classification of Malignant Epithelial Lung Tumors**2004****Preinvasive lesions**

- Squamous dysplasia/carcinoma in situ
- Atypical adenomatous hyperplasia
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Squamous cell carcinoma

- Papillary, clear cell, small cell, basaloid variants

Small cell carcinoma

- Combined small cell carcinoma

Adenocarcinoma

- Adenocarcinoma, mixed subtype
- Acinar adenocarcinoma
- Papillary adenocarcinoma
- Bronchioloalveolar carcinoma (nonmucinous, mucinous, mixed mucinous, and nonmucinous or indeterminate)
- Solid adenocarcinoma with mucin production
- Fetal adenocarcinoma
- Mucinous (colloid) adenocarcinoma
- Mucinous cystadenocarcinoma
- Signet-ring adenocarcinoma
- Clear cell adenocarcinoma

Large cell carcinoma

- Variants
 - Large cell neuroendocrine carcinoma
 - Combined large cell neuroendocrine carcinoma
 - Basaloid carcinoma
 - Lymphoepithelioma-like carcinoma
 - Clear cell carcinoma
 - Large cell carcinoma with rhabdoid phenotype

Adenosquamous carcinoma**Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements**

- Carcinomas with spindle and/or giant cells (pleomorphic, spindle cell, giant cell carcinoma)
- Carcinosarcoma
- Pulmonary blastoma
- Other

Carcinoid tumor (typical, atypical)**Carcinomas of salivary gland type** (mucoepidermoid carcinoma, adenoid cystic carcinoma, others)**Unclassified carcinoma**

Source: From Refs. 89 and 146.

mild to moderately atypical cells that line the alveoli without the presence of underlying interstitial inflammation and fibrosis (129). AAH has been associated with k-ras mutations. Additionally, overexpression of p53 has been reported in AAH, with accumulation of p53 proteins positively correlating with increasing grades of AAH and p53 mutations as AAH progresses towards BAC (90,129,130). The genetic alterations that lead to carcinogenesis from AAH to BAC remain unclear. AAH has been reported as measuring less than 1 cm with pure ground-glass

attenuation, (131,132). On CT imaging, the appearance of solid components and/or the increase in nodule size should raise concern for BAC (91,95,133). AAH has not been characterized on FDG PET to date.

Other preneoplastic entities have been incorporated into the WHO classification such as squamous cell dysplasia and carcinoma in situ, an entity discovered on white-light and autofluorescence bronchoscopy and not typically identified radiographically (134). Diffuse idiopathic neuroendocrine carcinoma is a very rare form of preneoplasia in which small neuroendocrine cells proliferate in the epithelium lining, the bronchi, and potentially involve the adjacent interstitium (89,135). Slow progression has been noted with development of carcinoid tumors. CT reveals small nodules and thickened bronchiolar walls with air trapping on CT (136). Bronchiolar fibrosis may also be present (129,137).

Carcinoid tumor

Carcinoid tumors are a subset of lung cancers that are neuroendocrine in nature (138). (Table 8) Low-grade typical, intermediate-graded atypical, and two types of high-grade tumors, large cell neuroendocrine carcinomas (LCNEC) and small cell lung carcinoma (SCLC), comprise the neuroendocrine spectrum. Typical and atypical carcinoids are categorized as carcinoids, while LCNEC is considered a subtype of large cell carcinoma, and SCLC as an independent category.

Typical carcinoid tumors lack necrosis and less than 2 mitoses per 2 mm², while atypical carcinoids contain 2 to 10 mitoses/2 mm² or necrosis (139). Carcinoid tumors (Table 3) typically manifest as round nodular densities with sharply demarcated borders that are centrally located and associated with the airways. Often endobronchial, the margins of the lesion may form acute angles with the wall of the airway, leading to obstruction (Fig. 30). Lesions may also deform and narrow a bronchus. Atelectasis can be present distal to a central carcinoid with varying degrees of consolidation that may be infectious or postobstructive pneumonitis (140). Mucoïd impaction distal to a lesion causing airway obstruction is suggestive of a longer standing process that can occur with a slow growing, long persisting lesion that may be benign or carcinoid in nature.

Table 8 Neuroendocrine Tumors

Neuroendocrine tumors	Category of tumor
Carcinoid	Carcinoid
Atypical carcinoid	Carcinoid
Large cell neuroendocrine carcinoma	Large cell carcinoma (non-small cell lung cancer)
Small cell carcinoma	Small cell carcinoma

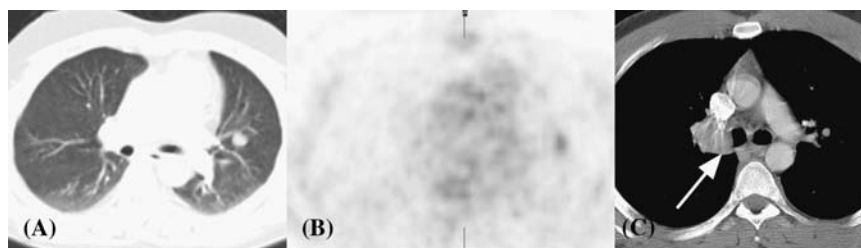


Figure 30 Carcinoid tumor. A 38-year-old man with a newly discovered solitary pulmonary nodule. (A) CT image from the PET/CT performed to further characterize the nodule shows a well demarcated, centrally located nodule with fairly smooth borders. The PET (B) shows mild-to-moderate uptake with an SUV of 3.1. Pathology showed a carcinoid tumor. (C) Endobronchial carcinoid in another patient occluding the orifice of the right upper lobe bronchus (arrow).

Carcinoid tumors can arise in the trachea also. Calcifications are identified in up to 30% of tumors, and these calcifications may be punctuate or diffuse. A smaller proportion, or approximately 16% to 40%, of carcinoids occur in the peripheral lung (140). Peripherally located carcinoids are typically round or ovoid with smooth or mildly lobulated borders (Fig. 30). Thin CT sections obtained through the lesion help define the lesions relationship to any associated bronchi. Upon intravenous contrast administration, intense enhancement is identified and helps delineate the lesion from postobstructive atelectasis or pneumonitis. Reactive adenopathy may be present with occasional metastases from typical and atypical carcinoids (141,142). Only 10% to 15% of patients with typical carcinoids will show lymph node metastases (143).

Atypical carcinoids tend to be more peripheral in the lung (144). Atypical carcinoid tumors are generally larger, behave more aggressively than typical carcinoid tumors, and frequently metastasize to regional nodes (66% of cases), lung, liver, and bone (139). Paraneoplastic manifestations such as carcinoid syndrome (cutaneous flushing, bronchospasm, chronic diarrhea, and valvular heart disease) and Cushing's syndrome are rare and are more commonly associated with atypical tumors (145).

Only two small series of pulmonary carcinoid tumors evaluated by FDG have been reported (125,145). Erasmus et al. studied seven patients, three with carcinoid tumors presenting as endobronchial masses and confirmed histologically as typical carcinoids, visually negative on PET. Three others presented on CT as smoothly marginated pulmonary nodules ranging in size from 1.5 to 3.0 cm in diameter, two of which were typical while one was atypical in histology. The calculated SUV for all the lesions ranged from 1.6 to 2.4. The last lesion was very large (10-cm mass) and was also found to be a typical carcinoid, but had an SUV of 6.6.

A more recent study by Kruger et al. evaluated FDG PET/CT in the diagnosis of pulmonary carcinoid tumors (125). Thirteen patients with solitary pulmonary nodules found to be pulmonary carcinoid tumors (12 typical,

1 atypical) were analyzed retrospectively. The size of the lesions ranged from 1.1 to 5.0 cm. Mean SUV of 18F-FDG in the typical carcinoids was 3.0 ± 1.5 (range 1.2–6.6); SUV in the only atypical carcinoid was 8.5. The SUV was less than 2.5 in 6 of 12 patients with typical carcinoids (50%) but the mean lesion size was larger in this study than in the series by Erasmus et al. (145). Both studies confirmed that FDG uptake in pulmonary carcinoid tumors is often lower than expected for other malignant tumors. Since carcinoids demonstrate a range of SUV uptake, surgical resection or biopsy of lesions suspected to be carcinoids should be considered. In fact, a sizeable pulmonary lesion on PET/CT without significant uptake and suspicious morphological characteristics on CT should raise the question of a carcinoid.

Primary Lung Cancer

Primary lung cancer is divided into small cell and non-small cell entities. The understanding of the pathology of lung cancer is evolving, leading to revisions in the WHO lung cancer staging in 1999, and only small changes in 2004, primarily in the criteria for the diagnosis of BAC (89,146). Non-small cell neoplasms comprise many histological entities (Table 7), although the major cell types encountered in clinical practice is adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell lung carcinoma. Primary lung malignancy manifests as a soft tissue nodule or mass demonstrating features suspicious for malignancy, as described earlier. Primary lung cancer typically spreads via the lymphatics to the mediastinum, and, therefore, adenopathy along the expected course for lymphatic drainage of a portion of the lung involved by a lesion suspicious for a primary lung malignancy is concerning for metastatic disease. Metastatic disease from a non-lung thoracic or extrathoracic malignancy does not typically demonstrate a predisposition toward one side of involvement or the other, although it remains a consideration particularly in an individual with an already known malignancy.

Histology and PET/CT of the Primary Tumor

Non-small cell lung cancer

With the exception of some BACs and carcinoid tumors, increased uptake on FDG PET imaging is seen for a majority of non-small cell lung cancer (NSCLCa). FDG uptake is related to cell proliferation rather than cellular density in NSCLCa (97) and has been correlated to tumor growth and prognosis. The solid adenocarcinomas, squamous, and large cell malignancies cannot be consistently differentiated on CT or FDG PET. Some CT characteristics have been associated with cell types but are not very predictive, perhaps except for the mixed adenocarcinoma with BAC component or BAC subtypes of adenocarcinoma (Table 9).

Adenocarcinoma and BAC. Adenocarcinoma accounts for the largest proportion of lung carcinomas, with approximately greater than 30% of all lung cancers being of this histology (89). Adenocarcinomas primarily include the mixed subtype, acinar (gland forming), papillary, BAC, and solid adenocarcinoma with mucin production (Table 7). Adenocarcinomas typically contain more than one subtype in approximately 80% of cases (129). The majority of adenocarcinomas are peripheral, manifesting as a nodular density with varying borders, and attenuation ranging from ground glass to solid attenuation. Central scarring in pulmonary adenocarcinomas with BAC-like pattern in the periphery of the tumor is not uncommon. In general, with the exception of BAC, these tumors are FDG-avid (147,148). Thus, in staging, assessment of tumor status is reasonably accurate with FDG PET alone (78% in one series) and comparable to CT (149).

BAC and mixed subtype adenocarcinoma with a BAC component. BAC is a form of adenocarcinoma that exhibits growth as a single layer of malignant cells without evidence of interstitial or stromal invasion (termed lepidic), with mucinous, nonmucinous, and mixed or indeterminate subtypes. Approximately 41–60% are mucinous, which tend to be multicentric, while 21% to 45% do not produce mucin, and tend to be solitary (89). Mixed BAC comprises 12% to 14% of cases, (89). Many invasive adenocarcinomas demonstrate a component of lepidic growth around the periphery. Emphasis, therefore, has been placed on the complete histologic sampling of a

tumor when a BAC component is present so that any areas of invasion, i.e., invasive adenocarcinoma, can be excluded to ensure appropriate characterization of a lesion as solely representing BAC rather than an adenocarcinoma with BAC components. The criteria for diagnosis of BAC is now reflected in the 2004 revision in WHO classification of these tumors (146). The final diagnosis of BAC can only be made on examination of the surgical specimen, and the emphasis of the lack of invasive growth as an essential criterion for characterizing adenocarcinoma as BAC may require reassessment of previous literature, given that more invasive cancers may have been previously characterized a BAC. BAC generally can be divided also into two separate clinical entities: focal and multifocal (diffuse) (150). The focal variety has a better prognosis than other forms of lung cancer, whereas the multifocal form tends to behave aggressively, with a resultant poor prognosis (41,151). Solitary BAC has been shown to have a longer doubling time and a slower rate of proliferation than other forms of lung cancer (152).

Several reports of negative FDG PET studies, most notably in patients with focal BAC of the lung (84,153,154) are explained by the relationship of FDG uptake to cell proliferation rather than cellular density in NSCLCA. Higashi et al. reported a series of seven patients with solitary BAC in whom 57% of FDG PET scans were negative (97). Solitary BAC showed a significantly lower peak standardized FDG uptake value compared with other cell types of lung cancer (153). Thus, FDG PET imaging may be insensitive for detecting BAC while correctly reflecting the proliferative nature of BAC. A recent study (85) of 15 patients, 7 with multifocal disease and 8 with unifocal histologically proven BAC, were evaluated with FDG PET. The nodules ranged in size from 0.5 to 5 cm in diameter (average 2.1 cm). 86% of the patients with multifocal BAC had positive PET scans and 62% of the subjects with solitary BAC had negative PET scans. The sensitivity for unifocal tumors was only 38%. This work supports the concept that the multifocal BAC manifests a different biologic behavior than the unifocal form, despite a similar histopathology.

Therefore, in the scenario of low FDG uptake, the appearance of a nodular density containing ground-glass

Table 9 Common Imaging Characteristics According to Histologic Type for Primary Lung Malignancy

Histology	Imaging appearance	PET imaging	Distribution
Adenocarcinoma	Ground glass to solid	Low to high metabolic activity	Peripheral
Squamous	Solid, cavitary	Increased	Central
Large cell	Solid, necrotic, large	Increased	Peripheral
Small cell	Solid, necrotic	Increased	Central

opacity with varying degrees of solid attenuation on CT is suggestive of BAC or adenocarcinoma with BAC components. Focal BAC is now detected more frequently in the past, and manifests ranging from the solitary or multiple nodules (Fig. 19). The nodules may be pure ground-glass, part-solid and part ground-glass nodules, and solely solid nodules with air bronchograms and pseudocavitation (95,155). In general, subsolid nodules with greater solid components correspond to aggressive features of adenocarcinoma (156). Multiple nodules may be multicentric or associated with a dominant nodule with satellite nodules (146). Diffuse disease may entail nonsegmental and lobar consolidation that has been termed the “pneumonic” form of BAC, mimicking pneumonia (Fig. 20). In this scenario, the presence of nodules and a peripheral distribution may be helpful for differentiation of BAC from pneumonia (157). Symptomology and the duration of findings are very useful for differentiating pneumonic BAC and pneumonia. Individuals with BAC are often afebrile, and those with significant multifocal BAC may have bronchorrhea, when copious secretions that contain tumor cells, typically mucinous, are expectorated (158–160).

In a study by Mirtcheva et al. (96), the imaging features of BAC and adenocarcinoma with BAC were contrasted. BAC more frequently had a ground-glass halo surrounding a solid opacity, often presented as a ground-glass opacity mixed with consolidation, or was a pure ground-glass nodule. On the other hand, adenocarcinoma with BAC features most commonly had a ground-glass opacity mixed with consolidation and less frequently had a ground-glass halo. Rarely did adenocarcinoma with BAC have superimposed lymphangitis manifesting as thick linear reticular densities. In this study by Mirtcheva, pure uniform ground-glass opacity and absence of lymphangitis was the most useful for differentiating BAC from adenocarcinoma with BAC. Air bronchograms were identified in 67% of the BACs and 64% of the adenocarcinomas with BAC (96).

The differentiation of BAC from adenocarcinoma with BAC features on imaging may significantly impact patient care as a better understanding of the management of the two lesions is acquired. Noguchi et al. demonstrated a 100% five-year survival for their patients with small adenocarcinomas with pure BAC histology and no invasion (Noguchi Type A and B), while those with mixed BAC and invasive adenocarcinoma (Noguchi Type C) had a survival rate of 74.8% and purely invasive adenocarcinoma (Type D) that of 52.4% (161). In the Japanese literature, it has been proposed that nodules of pure ground-glass attenuation be resected using a limited resection as opposed to a lobectomy, although further understanding of the relationship between survival and limited resection is needed (162,163). The degree of central fibrosis in a lesion on histopathology is prognostically important in terms of

survival, with a five-year survival of 100% associated with scars less than or equal to 5 mm (164). Takashima et al. reported that lesions less than 14 mm, ground-glass attenuation greater than 57%, and Noguchi type A or type B adenocarcinomas (BACs) were associated with better survival (156). Kodama et al. showed that patient's nodules comprising greater than 50% ground-glass attenuation did not have diagnosed relapse by the time of the publication of their results (165).

In summary, nodules containing ground-glass attenuation are suspicious for adenocarcinoma, either BAC, adenocarcinoma with BAC features, or the premalignant entity atypical adenomatous hyperplasia. Any solid component within a nodule containing ground glass should raise suspicion of more aggressive forms of BAC or adenocarcinoma with BAC features. FDG uptake in multifocal BAC correlates with tumor growth and indicates a more aggressive behavior and poorer prognosis. Either poor prognostic CT characteristics or the presence of FDG uptake should dictate a more aggressive approach to management.

Squamous cell carcinoma. Squamous cell cancer has now been surpassed by adenocarcinoma in terms of frequency. Variants of squamous cell carcinoma include papillary, clear cell, small cell, and basaloid. The majority of squamous cell tumors are central, arising in the segmental bronchi, while approximately one-third of the lesions appear peripherally. Intercellular bridging, squamous pearl formation, and individual cell keratinization are identified typically in the well-differentiated squamous cell tumors, although these features may be more difficult to identify in the poorly differentiated tumors (89,129). On CT, squamous cell cancers can exhibit cavitation suggesting necrosis as is seen on FDG PET as well (Fig. 31). Given their central location, airway obstruction can occur with spread along the more proximal airways. Peripheral squamous cell carcinomas have been shown to manifest with well-defined, lobulated margins and fine spiculations (166). On FDG PET, squamous cell carcinomas are more FDG-avid than other non-small cell types of lung cancer (147). Relatively, hypoactive centers of these tumors are more commonly identified in squamous cell carcinoma than most other lung cancers (167). The low activity may correlate with necrosis and cavitation. Rarely, false-negative PET scans have been reported, but usually in early stage disease (148).

Large cell carcinomas. Large cell carcinomas comprise approximately 9% of lung carcinomas. These lesions typically occur in the periphery of the lung. Large cell carcinomas often have necrotic areas and are large in size, comprising sheets and nests of large polygonal cells. The cells contain vesicular nuclei and prominent nucleoli (89). A lack of squamous or glandular differentiation is identified on light microscopy. Variants include large cell

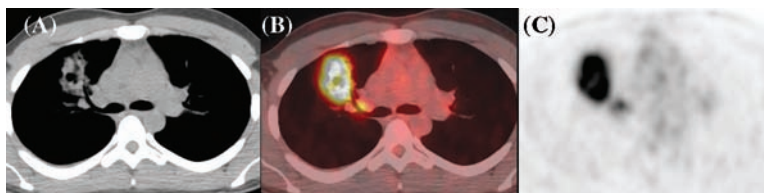


Figure 31 Squamous cell lung carcinoma. (A) CT with soft tissue windows from the PET/CT shows an irregular density with cavitation that fuses (B) to markedly increased metabolic activity (SUV 10.3) on the PET that extends into the right hilum with uptake in right hilar nodes (C).

neuroendocrine, basaloid, lymphoepithelioma-like clear cell, and large cell with rhabdoid phenotype. Necrosis seen as centrally decreased activity is frequently identified on FDG PET in these tumors (167).

LCNEC is considered part of the neuroendocrine tumor spectrum, yet considered a subtype of large cell carcinoma (89,129). LCNEC has greater than 10 mitoses per 2 mm² and cytological features of large cell carcinoma (129). Polygonal cells with abundant cytoplasm and prominent nucleoli are most often seen (129). Neuroendocrine differentiation is required, as shown by immunohistochemistry, which can be demonstrated in conventional adenocarcinoma also (129).

Large cell-neuroendocrine tumors on CT appear as typically large lobulated masses without air bronchograms and calcifications. Inhomogeneous enhancement is related to necrosis in the larger lesions (168).

Small cell lung carcinoma

SCLCa is a member of the neuroendocrine carcinoma spectrum. SCLCa accounts for approximately 20% of all lung cancers in the past, currently 13.8% of lung cancers (89,169). These tumors have greater than 10 mitoses per 2 mm² and small cell cytological features (129). On histology, cells have scant cytoplasm, small size, round to fusiform shape, fine granular nuclear chromatin, and lack or have inconspicuous nucleoli (89). Pure SCLCa and combined SCLCa comprise the SCLCa category (89). Combined SCLCa makes up about 10% of SCLCa. The term applies when a mixture of any non-small cell type is present along with SCLCa (89). SCLCa presents as a perihilar mass, typically in a peribronchial locations. The bronchial submucosa and peribronchial tissue are infiltrated by tumor, leading to compression of the bronchi.

On imaging, these tumors occur in a perihilar central location and lead to extensive lymphadenopathy from metastatic disease. Necrosis is frequently present, and distal atelectasis and pneumonitis accompany the central lesions. Occasionally, the primary lesion may not be evident, and difficult to differentiate from hilar adenopathy (170). Primary tumor or adenopathy can cause compromise of the recurrent laryngeal and phrenic nerves with subsequent vocal cord and diaphragmatic paralysis,

respectively. Superior vena cava syndrome results from compression by mediastinal adenopathy. Extrathoracic metastases are common, occurring in 60% to 70% of cases (140).

FDG PET has a greater role in staging than in detection of SCLCa, but when patients present with paraneoplastic neurological syndromes, FDG PET has played a significant role in identifying a potential biopsy site for diagnosing the presence of the underlying SCLCa (171–173). FDG PET and CT have been shown to be complementary in identifying the primary SCLCa (171) with a 90% sensitivity for PET increasing to 100% when combined with CT. Associated paraneoplastic syndromes include limbic encephalitis, encephalomyelitis, paraneoplastic cerebellar degeneration, and sensory neuropathy and are usually related to anti-HU antibodies or anti-CV2 antibodies in patients with SCLCa (172). Lambert-Eaton myasthenic syndrome has also been described in association with SCLCa (174).

Lung Cancer Staging

A staging system for lung cancer seeks to standardize the description of the extent and spread of the primary tumor serves as a method for stratifying individuals with lung cancer into groups with similar prognosis. Staging therefore aids in directing patient treatment.

Non-Small Cell Lung Cancer Staging

The staging of an individual with NSCLCa entails assessment of the primary tumor in terms of invasion and involvement of vital local structures (T status) and evaluation for spread of tumor to hilar and mediastinal nodes (N status) or distant locations (M status) (Table 10). The staging system for NSCLCa has evolved as more information concerning tumor patterns and patient survival has been gained. Currently, the 1997 revision of the International Staging System for Non-Small Cell Lung Cancer is in use (175). In this revision, stages I and II each were divided into A and B categories. The stage T3N0M0 was categorized as to stage IIB rather than IIIA, and a satellite

Table 10 T, N, M Descriptor Definitions in the 1997 International Staging System for Non-Small Cell Lung Cancer

Primary tumor (T)	
Tx	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i>
T1	≤3 cm in greatest dimension, surrounded by lung or visceral pleural, without bronchoscopic evidence of invasion, not involving the mainstem bronchi
T2	Tumor >3 cm or involving a mainstem bronchus yet 2 cm or greater distance from the carina or involving the visceral pleura or associated with atelectasis or postobstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor invading chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium, mainstem bronchus within 2 cm of, although, not invading the carina or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor invading mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina or tumor with malignant pleural or pericardial effusion or satellite tumor nodule within the same lobe as primary tumor
Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar nodes, and intrapulmonary nodules involved by direct extension of primary tumor
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis to contralateral mediastinal, contralateral hilar, or ipsilateral or contralateral scalene (i.e., supraclavicular) lymph nodes
Distant metastasis (M)	
Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Source: From Ref. 189.

nodule representing tumor in the same lobe was classified as T4 (Table 11). Individuals with a primary tumor with one or more synchronous lesions within different lobes are considered M1.

Table 11 Stage Grouping in the 1997 International Staging System for Non-Small Cell Lung Cancer

Staging	
0	Carcinoma in situ
IA	T1, N0, M0
IB	T2, N0, M0
IIA	T1, N1, M0
IIB	T2, N1, M0
	T3, N0, M0
IIIA	T3, N1, M0
	T3, N2, M0
	T2, N2, M0
	T1, N2, M0
IIIB	Any T, N3, M0
	T4, N0, M0
	T4, N1, M0
	T4, N2, M0
IV	Any T, Any N, M1

Tumor (T) staging

The T descriptor in the TNM staging pertains to assessment of the primary tumor and its local extent (Table 10). Determining factors for T staging are the tumor size and invasion of mediastinal, pleural, chest wall, and bronchial structures. A T1 descriptor is assigned to those tumors that are 3 cm or less, those fail to invade a bronchus proximal to the lobar level, and are surrounded by lung or visceral pleura. T2 tumors are those that are greater than 3 cm, invade the visceral invasion, invade bronchi proximal to the lobar level yet are more than 2 cm distal to the carina, or are associated with atelectasis or obstructive pneumonitis that does not involve the entire lung. T3 lesions are tumors of any size that invade the chest wall, diaphragm, mediastinal pleura, parietal pericardium, or the bronchi less than 2 cm distal to the carina but not involving the carina. Atelectasis or obstructive pneumonitis of the entire lung is also considered a T3 characteristic. A T4 tumor is any tumor that invades the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina. A malignant pleural or malignant pericardial effusion or a satellite nodule that is tumor within the same lobe as the primary lung cancer is also deemed T4.

Tumor status is primarily determined by CT, where the tumor and adjacent structures (pleura, mediastinal fat, pericardium, heart, vasculature, chest wall, lobe in which tumor is located) are scrutinized. The administration of intravenous contrast is suggested for initial staging. When assessing T status, intravenous contrast improves the differentiation of atelectatic lung from central tumor, and the interface between tumor in the mediastinum, adjacent vessels, and heart can be assessed with greater confidence.

On CT, visceral invasion, and therefore T2 disease, is suspected when focal pleural thickening is noted adjacent to a tumor that abuts the pleura. Increased FDG uptake oriented along the pleura adjacent to the tumor suggests pleural involvement. Chest wall involvement and T3 disease is suggested when tumor extends beyond the confines of the pleural space, infiltrating into and obliterating the extrapleural fat. Involvement of the adjacent intercostal musculature and osseous structures are also indicators. Two other criteria suggestive of invasion are a broad base of contact greater than 5 cm and an obtuse angle formed by the tumor and adjacent pleural surface (176,177). Sensitivity and specificity for chest wall invasion for CT was reported as 87% and 59%, respectively, by Glazer et al. using these criteria (177). Suzuki et al. in 19 cases of chest wall invasion reported a sensitivity of 68% and specificity of 66%. The lower sensitivity and specificity for CT and chest wall invasion relate to the fact that a broad base of contact of a tumor with an adjacent structure is not indicative of tumor infiltration. Alternatively, microscopic involvement of a structure may be overlooked with CT imaging (178).

Similar concepts are used when assessing for mediastinal invasion. Stranding in the mediastinal fat in contiguity with a tumor and loss of the mediastinal fat planes adjacent to a tumor contacting the mediastinum is suggestive of at least T3 involvement. A pericardial effusion or thickening contiguous with the primary tumor with uptake on PET/CT conforming to the contour of the pericardium should raise suspicion for T3 disease. CT for assessing mediastinal invasion has been reported to have varying sensitivity and specificity, described on the order of 50% to 52% and 82% to 89%, respectively (179). Criteria that have been proposed as predictive of a tumor that is resectable include tumor: (i) having less than 3 cm of contact with the mediastinum, (ii) contacting less than one-fourth or 90° of the circumference of the aorta, and (iii) preserving the fat plane that is usually seen near the aorta and other mediastinal vessels (180). However, investigation has shown that these criteria are not reliable. Therefore, the possibility of resection of the tumor should not be denied in patients with lesions with these characteristics.

Thin section imaging and MPRs improve the ability to assess for invasion of the chest wall and mediastinum. Using thin section imaging and a soft detail algorithm, Uhrmeister et al. more recently reported improved sensitivity and specificity over 10 mm standard CT sections for chest wall invasion (176). Although a study by Higashino et al. did not demonstrate improved detection of mediastinal invasion with MPRs from multidetector CT, the authors reported a significant benefit for chest wall invasion (181).

T4 designation is assigned when vertebral body destruction by direct extension from the primary lung lesion in addition to infiltration of soft tissues in the vicinity such as the neural foramina. Intraspinal involvement is best assessed using MRI. Any nodule of increased uptake on PET/CT in the same lobe as the primary tumor raises suspicion for a satellite tumor. However, a satellite nodule may be difficult to differentiate from segmental or subsegmental nodes, which are typically located adjacent to bronchi.

Nodal (N) staging

The N staging indicates whether regional nodal metastases are present. N1 descriptor is used when there are peribronchial or hilar lymph nodes on the same side as the primary tumor or intrapulmonary nodes involved by direct extension of the primary tumor. N2 disease is assigned when nodes in the mediastinum are located on the same side as the primary tumor or in the midline position. N3 disease is present when tumor has spread to nodes in the contralateral or ipsilateral hilar regions in addition to the ipsilateral or contralateral scalene or supraclavicular lymph nodes.

Nodal metastases are present at time of diagnosis of lung cancer in approximately 26% to 44% of patients (182). Nodal involvement has been shown to be a significant prognostic indicator. While nodal disease typically spreads to the ipsilateral hilar nodes prior to involving the mediastinal nodes, it has been shown that N2 or ipsilateral mediastinal nodal disease can occur without N1 hilar involvement, termed skip metastasis (183,184). Okada et al. reported a 22% incidence of skip metastasis, (183). Subcarinal lymph node involvement has been associated with a worse prognosis (185–188). Mediastinal nodal spread has been associated with larger masses and central lesions in the inner one-third of the lung. Left lower lobe lesions have a tendency to spread contralaterally (182).

To better standardize the surgical and radiological reporting of nodal disease for lung cancer staging, a consensus statement defining the nodal locations in the mediastinum and hilar regions was adopted by both the American Joint Committee on Cancer (AJCC) and the Union

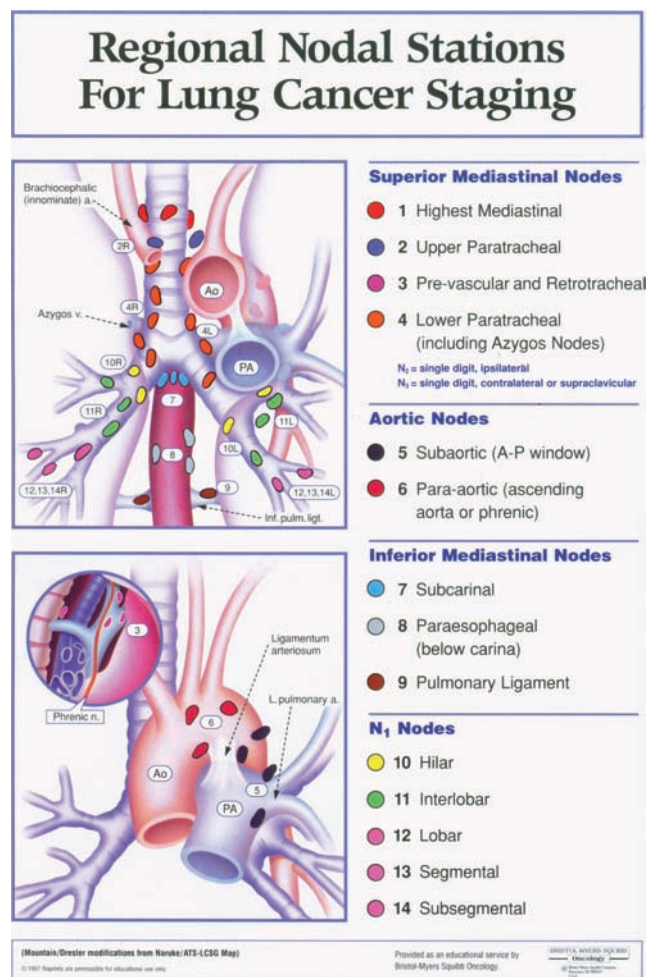
Internationale Contre le Cancer (Figs. 32–34). The consensus statement was published at the same time as the revisions to the International Staging System for Non-Small Cell Lung Cancer in 1997 (189,190). The regional lymph node station map combined features of two preexisting nodal staging systems that had been used over the past 10 years, the Naruke system, which had been approved by the AJCC, and the classification of the American Thoracic Society and the North American Lung Cancer Study Group (ATS-LCSG). The resultant nodal station classification classifies nodes in relationship to “mediastinal pleural envelope” to demarcate mediastinal nodes from hilar nodes, as in the Naruke classification, and also the relationship of nodes to anatomic landmarks that was utilized in the ATS-LCSG system (186,191). A common system ensures that lymph nodes are more precisely localized and minimizes variations in reporting of nodal involvement. Staging, management, and research results can be thus shared and compared easily, regardless of institution.

The major landmarks used for nodal staging are the superior aspects of the left brachiocephalic vein, aortic arch, and mainstem bronchi. Other anatomic structures that are utilized include the more distal bronchi, the ligamentum arteriosum, and the inferior pulmonary ligaments. The midline of the trachea in the mediolateral dimension is used as the landmark for differentiating right or “R” from left-sided or “L” nodes. Nodes are then considered either ipsilateral or contralateral if they are on the same or opposite sides, respectively, as the side of the primary tumor. Lymph nodes centered directly anterior to the trachea and in the subcarinal region are considered midline and, therefore, ipsilateral disease.

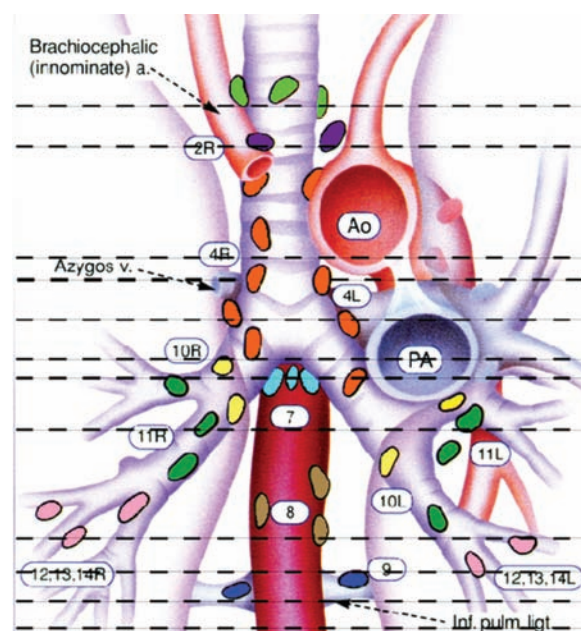
A major goal of the nodal classification system is to differentiate nodes in the hilum and lung from their mediastinal counterparts. In the nodal classification, mediastinal nodes are assigned single-digit numbers while nodes in the hilum and distal to this level have double-digit numbers. Station 10 hilar nodes are differentiated from lower paratracheal mediastinal nodes (station 4) by a line drawn tangent to the superior aspect of the upper lobe bronchi. These nodes are not accessible to mediastinoscopy but can be sampled occasionally using trans-bronchial/transcarinal techniques.

The discrimination of aortopulmonary, also termed subaortic (station 5) lymph nodes, from the lower left paratracheal nodes (station 4) is of clinical importance (Fig. 33). Appropriate labeling of these nodes aids in

Figure 32 Regional nodal station map for lung cancer staging (A). (B) Adaptation of part of figure in A in which nodal colors have been adjusted in some areas for easier depiction of different stations and correspond with colorings on enlarged nodes in CT images in the remaining images (601).



(A)



(B)

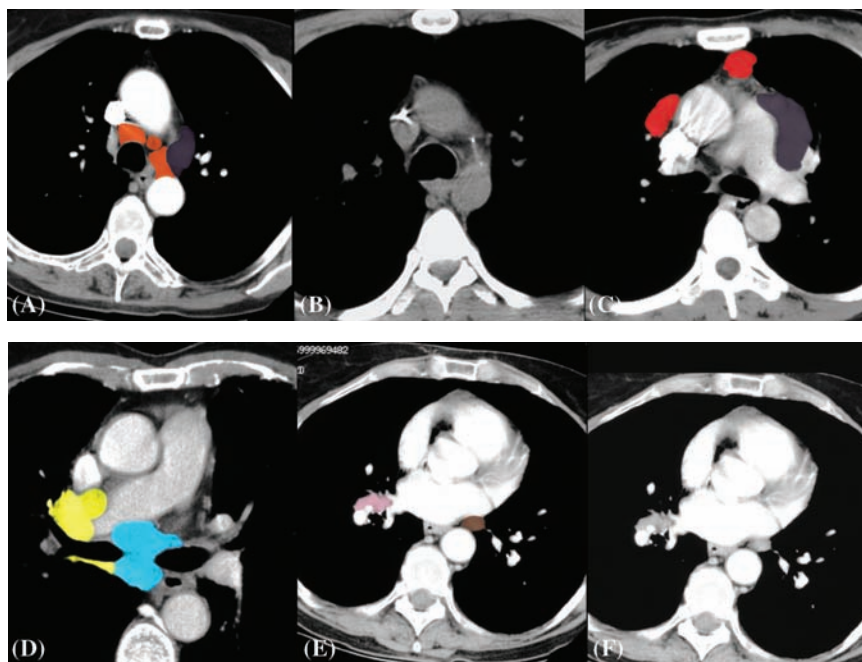


Figure 33 (A) At the level of the aorticopulmonary window, the station 4 lower left paratracheal (orange) nodes are delineated from the station 5 subaortic (dark purple) nodes by the ligamentum arteriosum that courses from the posterior aspect of the aortic arch to the superior aspect of the main pulmonary artery. The ligamentum is depicted in image (B) where it is partially calcified. In (C) the station 6 paraaortic or phrenic nodes are colored (red). The subaortic node (dark purple) is also shown. In (D), the station 10 right hilar nodes (yellow) are below the level of the superior aspect of the upper lobe bronchi and are shown with mediastinal station 7 subcarinal nodes (blue). In (E,F), right-sided station 12 nodes at the segmental level in addition to station 9 inferior pulmonary ligament nodes on the left.

decision making for potential biopsy approaches. Station 5 nodes are located lateral to the ligamentum arteriosum, which runs from the underside of the distal aortic arch toward the superior aspect of the main pulmonary artery. Station 4L nodes are located medial to the ligamentum arteriosum and are accessible to cervical mediastinoscopy, while station 5 nodes typically require an anterior mini-thoracotomy or video assisted thoracoscopic biopsy (VATS) procedure for sampling. Station 3 prevascular and 6 paraaortic nodes, given their anterior location are also sampled by these means. Station 3 prevascular and station 6 lymph nodes lie anterior to the great vessels above or below, respectively, a line tangential to the superior aspect of the aortic arch. Nodes in the retrotracheal region are also termed station 3. Station 7 nodes are in the subcarinal region, while station 8 paraesophageal nodes lie more caudal to these nodes. The differentiation of subcarinal from paraesophageal nodes may be difficult.

Noninvasive staging of nodal disease, CT and PET. A number of approaches exist for determining whether nodes are involved by tumor (Table 12). Clinical staging of nodal disease includes noninvasive, minimally invasive techniques, and invasive techniques, excluding formal

lymph node sampling (192). Noninvasive techniques include chest radiography, CT, MRI, and PET with or without CT. Minimally invasive techniques include bronchoscopy with transbronchial or carinal needle aspiration (TBNA) with or without endobronchial ultrasound, trans-thoracic needle aspiration biopsy (TTNAB), transesophageal ultrasound guided fine needle aspiration biopsy. Invasive techniques include mediastinoscopy with or without extended cervical mediastinoscopy, mediastinotomy with or without VATS, thoracotomy with intraoperative frozen section, mediastinal sampling or dissection, and mediastinal sentinel lymph node mapping.

For years, CT of the chest has been the standard noninvasive method for staging the mediastinum using size as criteria for evaluating possible malignant involvement. Lymph nodes that are greater than 1 cm in short axis on CT raise suspicion for nodal metastases. The use of this criterion on CT, however, has been associated with sensitivities and specificities of 64% and specificity of 62% by McLoud et al. (193). The Radiological Diagnostic Oncology Group prospective data showed a sensitivity and specificity of thoracic CT of only 52% and 69%, respectively (194).

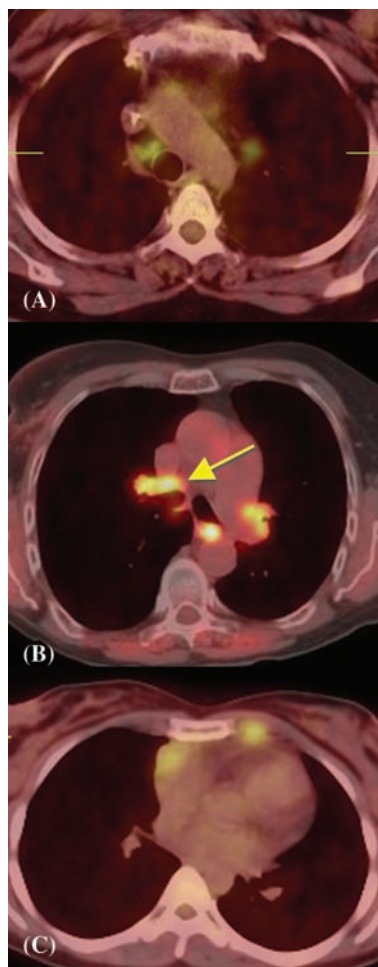


Figure 34 (A) Fused PET/CT shows activity in paraaortic (station 6) lymph nodes and right paratracheal (station 4R) nodes. (B) Right hilar (station 10) nodes confluent with station 4R nodes (*arrow*) and left hilar (station 10) nodes demonstrate metabolic activity on the fused image. A lymph node adjacent to the esophagus near the subcarinal region is also active. (C) Lower fused PET/CT section shows activity in anterior mediastinal lymph nodes in the pericardial region.

Other studies have demonstrated the need for additional evaluation of the mediastinum for staging (195–197). More recently, a search of MEDLINE, Health-Star, and Cochrane Library databases between 1991 and 2001, and of print bibliographies by Toloza et al. demonstrated CT to have a pooled sensitivity of 57% for and specificity of 82% for staging the mediastinum (198). The low specificity of CT is related to reactive lymph node enlargement that can occur, particularly in the setting of a postobstructive pneumonitis, in which 40% of enlarged lymph nodes suspected to be malignant prove to be benign (182). The low sensitivity of CT is associated with the inability to identify microscopic metastasis to lymph

nodes, occurring in 15% of patients who undergo complete mediastinal lymph node dissection (182).

A large number of prospective studies comparing the performance of CT and PET in mediastinal lymph node staging have shown PET to be more accurate than CT (199–203). In a study by Vansteenkiste et al., the overall accuracy of FDG PET in the detection of mediastinal lymph node involvement was 90% (range 78–100) with a sensitivity of 89% (range 67–100) and a specificity of 92% (range 79–100). CT was only accurate in 65% (range 20–86) of the cases with a sensitivity of 75% (range 52–79) and a specificity of 80% (range 43–90) (204). In the study by Toloza et al. that pooled studies between 1991 and 2001, the pooled sensitivity was 84% and specificity was 89% for staging the mediastinum, with PET (198). The superiority of PET over CT in mediastinal lymph node staging has been confirmed in different meta-analyses (205–207).

Given the performance of PET in excluding disease in the mediastinum, researchers in the PET in Lung Cancer Staging Trial compared conventional radiological staging with the same staging without PET in a randomized controlled trial (208). The authors suggested that the noninvasive evaluation with PET might replace mediastinoscopy, the gold standard invasive approach, and curative surgical resection could be performed without pathologic confirmation. The addition of PET would prevent unnecessary surgery in one of five patients with suspected non-small cell lung cancer (NSCLC) (208). Given the high negative predictive value of PET for mediastinal lymph nodes, mediastinoscopy for noncentral tumors was felt to be unnecessary in the case of negative PET. No need for further mediastinoscopy was also the conclusion of another prospective study on 102 patients in case of negative findings on PET staging of the mediastinum (209).

Controversy, however, remains concerning whether a negative PET result obviates the need for mediastinoscopy (210–212) especially for patients with stage II and III disease. In a comparative study, mediastinoscopy showed less false-negative results (3%) compared with PET (11.7%) (213). False-negative results can occur with PET, as with CT, when the tumor load in the mediastinal nodes is minimal. This condition, sometimes called minimal N2 disease, has a moderately good prognosis after surgery. The number of nodes, number of levels of lymph node stations, and status of the nodal capsule require pathologic confirmation. Patients with minimal N2 disease benefit from neoadjuvant treatment prior to surgical resection. Minimal (histological) N2 disease or micro-metastatic disease cannot be imaged effectively on PET because of the spatial resolution; false-negative lymph nodes diameters range from 1 to 7.5 mm (214). False-negative findings may be also due to misregistration from respiratory, cardiac, and body motion. Hypermetabolic

Table 12 Sensitivity and Specificity of CT, PET, and PET/CT for Mediastinal Staging

Author (reference)	Sensitivity (%)	Specificity (%)	Accuracy (%)
CT nodal enlargement greater than 1 cm in short axis			
McLoud, 1992 (193)	64	62	
Dwamena, 1999 (207)	60	77	
Weng, 2000 (203)	73	77	76
Pieterman, 2000 (209)	75	66	
Vansteenkiste, 2001 (204)	75	80	
Reed, 2003 (199)	37	91	
Gould, 2003 (205)	61	79	
Cerfolio, 2003 (200)	71	77	76
Lardinois, 2003 (217)			59
Antoch, 2003 (215)	70	59	63
Takamochi, 2005 (214)	29	83	65
Increased uptake PET			
Dwamena, 1999 (207)	79	91	
Weng, 2000 (203)	73	94	87
Pieterman, 2000 (209)	91	86	
Fischer, 2001 (206)	83	96	
Toloza, 2003 (198)	84	89	
Vansteenkiste, 2001 (204)	89	92	
Gonzalez-Stawinski (213)	64.4	77.1	74.3
Reed, 2003 (199)	61	84	
Gould, 2003 (205)	85	90	
Cerfolio, 2003 (200)	43	75	68
Lardinois, 2003 (217)			49
Antoch, 2003 (215)	89	89	89
Takamochi, 2005 (214)	39	79	66
Halpern, 2005 (216)			69
PET/CT			
Lardinois, 2003 (217)			81
Antoch, 2003 (215)	89	94	93
Halpern, 2005 (216)			78

central tumors or hilar lymph nodes can decrease the detectability of small mediastinal lymph nodes (Fig. 35). This was illustrated in a recent survey of 400 patients, where PET was proved to be more likely to miss N2 disease in the subaortic and subcarinal nodes with central tumors or hilar lymphadenopathy (200).

Even though some studies have demonstrated a high positive predictive value for PET of 74% to 93% for evaluation of the mediastinum, a direct comparison of PET with mediastinoscopy showed a positive predictive value for PET of only 44.6% (213). False-positive results can occur in cases of anthracosilicosis (Fig. 10), infection, or granulomatous disorders since activated macrophages and inflammatory cells demonstrate increased glucose uptake. In patients with increased uptake, confirmation of N2 or N3 disease by mediastinoscopy is therefore indicated to ensure that no patient with resectable N0 or N1 disease is denied a chance of curative surgery.

In mediastinal lymph node staging, the question of whether fused images from integrated PET/CT scanners provide more accurate information than simple correlative reading of PET and CT is still open. Some data suggest no significant difference in accuracy between the two methods, in an analysis either by N stage or by individual lymph node stations (202). In contrast, for excluding disease in the mediastinum, other studies have shown that combined PET/CT had the highest accuracy and negative predictive value compared with CT alone, PET alone, and to visual PET/CT correlation (215–217).

Invasive staging of nodal disease. While in-depth description of minimally invasive and invasive techniques is beyond the scope of this text, an understanding of the pitfalls of these sampling methods is helpful for the noninvasive imager. The sensitivities and specificities of these minimally invasive and invasive procedures are affected by patient selection, given that individuals

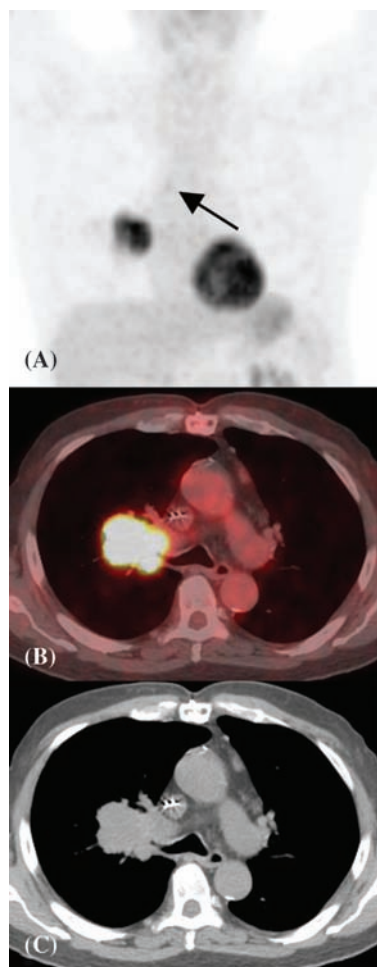


Figure 35 PET/CT performed for staging of newly diagnosed lung cancer. (A) Anterior view of a maximum intensity projection shows the large metabolically active right hilar mass with a suggestion of a faint lymph node uptake in the right paratracheal region (*arrow*). (B) CT scan shows the mass extending into the mediastinum with prevascular nodes. (C) The fused PET and CT shows minimal activity in the more anterior left paraaortic nodes and suggest that even the precarinal soft tissue is not active. At mediastinoscopy the prevascular nodes were involved with tumor.

without enlarged mediastinal nodes may not be selected for endoscopic ultrasound. TBNA has sensitivities and specificities of 76% and 96%, respectively. For staging the mediastinum in which subcarinal, paratracheal nodes, potentially aorticopulmonary window, and hilar nodes are sampled (182). Endobronchial ultrasound enables easy identification of vessels from nodes to aid in transbronchial biopsy (197,218). Endoesophageal ultrasound and transesophageal fine needle aspiration is typically performed as an outpatient with conscious sedation, and can be used to sample stations 5, 7, 8, and possibly 9. The sensitivities and specificities of endoesophageal ultrasound are 88% and 91%, respectively, in a review of

reported literature pertaining to invasive sampling (198). The roles of endoesophageal and endobronchial ultrasound will be better understood with further investigation.

Invasive surgical techniques include cervical mediastinoscopy, in which a cervical mediastinoscope is placed via an incision at the suprasternal notch and passed in the pretracheal fascia. Sampling of the paratracheal and subcarinal nodes can be performed with a sensitivity of 81% and specificity of 100%, respectively (198).

Extended mediastinoscopy and anterior mediastinotomy are procedures used to sample the anterior mediastinal nodes and aorticopulmonary window nodes. Extended mediastinoscopy includes sampling of stations 5 and 6 nodes, in which the scope is passed between the brachiocephalic artery and left common carotid artery over the aortic arch into the aorticopulmonary window (198). Mediastinotomy entails an anterior parasternal approach (Chamberlain procedure) region, typically at the level of the 2nd and 3rd intercostals space (198). The technique is more commonly performed through the left thorax, at which time only sampling of 5 and 6 nodes can be performed. The procedure can be performed through the right chest to sample stations 2R, 4R, and 3 lymph nodes (198).

Patients with enlarged nodes on CT or increased activity undergo nodal sampling by mediastinoscopy to stage individuals prior to resection (182). Lesions within the inner one-third of the lung parenchyma have a higher risk for N2 nodal disease. Left lower lobe lesions have a greater tendency to spread contralaterally, and therefore sampling of bilateral mediastinal nodes, including anterior nodes by mediastinoscopy in combination VATS or mini-mediastinotomy, is performed at certain centers (182). The use of mediastinoscopy to potentially detect micrometastases in negative PET/CT cases may vary according to institution.

Metastatic disease (M)

The observation of metastases in patients with NSCLC has major implications for management and prognosis. The presence of distant metastasis is classified as stage IV disease, which precludes a patient from the possibility of curative treatment. Forty percent of patients with NSCLC have distant metastases at presentation. Most commonly involved organs are the adrenal glands, bones, liver, and brain. After radical treatment for localized disease, 20% of patients develop an early distant relapse, probably because of systemic micrometastases that were present at the time of initial staging (219). FDG PET and now FDG PET/CT have accepted roles in the staging of distant metastases (220). PET will detect otherwise unknown metastatic disease leading to upstaging of the patient, as detected in 24% of patients in two different series (221,222) (Fig. 36).

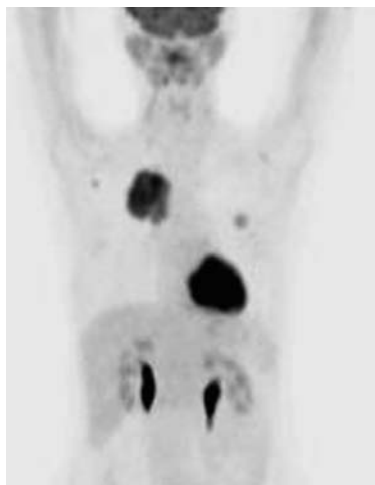


Figure 36 Maximal intensity projection view of a patient diagnosed with a stage IV right lung cancer with a pulmonary metastasis in the contralateral lung that had been found on an initial diagnostic CT and a previously unrecognized bone metastasis in a lateral upper right rib discovered on staging FDG PET.

Metastases to the adrenal gland. In up to 10% of patients with NSCLC, enlarged adrenal glands are visualized on CT at the time of presentation. Approximately two-thirds of these adrenal masses are benign (223,224), comprising mainly adrenal cortical adenomas, common benign tumors. Most adrenal adenomas are less than 4 cm in diameter (225). Attenuation of adrenal lesions on non-contrast CT has been used to differentiate adrenal adenomas from malignant counterparts (226). A meta-analysis by Boland et al. of 10 previously published studies reported a 71% sensitivity and 98% specificity for adenomas when using a maximal value of 10 HU on an unenhanced CT (227). The low attenuation of the adenomas is related to the intracytoplasmic fat. Korobkin et al. demonstrated that intracytoplasmic fat was inversely related to HU attenuation values on noncontrast CT (226). Lipid-poor adenomas comprise between 10% and 40% of adenomas (225) and cannot be characterized as adenomas on unenhanced CT. Their attenuation values overlap other adrenal soft tissue lesions.

Measurement of attenuation of adrenal lesions on contrast-enhanced CT is not reliable for differentiating metastases from adenomas on portal venous phase imaging, as there is significant overlap in imaging characteristics (228). Delayed imaging and measurement of washout of contrast from an adrenal mass, however, can be used to identify adenomas, which show more rapid washout than malignancies (225,228–230). This technique is useful for identifying lipid-poor adenomas, and is typically expressed as the percentage of enhancement washout [= (attenuation value at enhanced CT–attenuation value at

delayed enhanced CT)/(attenuation value at enhanced CT–attenuation value at unenhanced CT) $\times$ 100] or the relative percentage of enhancement washout [= (attenuation value at enhanced CT–attenuation value at delayed enhanced CT)/attenuation value at enhanced CT $\times$ 100]. Using a 60% percentage of enhancement washout at 15 minutes will yield a sensitivity of 88% and specificity of 96% (225,231). Relative enhancement washout threshold of 40% has a sensitivity of 96% and a specificity of 100% for the diagnosis of adenoma, while a threshold of 50% has been shown to result in a sensitivity and specificity of 100% (231).

Thus, a standard protocol for CT evaluation would include a noncontrast CT. If the mass is clearly lipid containing (HU <10), then further characterization is unnecessary (Fig. 37). Macroscopic fat visualized within an adrenal mass is suggestive of a myelolipoma. Adrenal cysts are less common lesions that are low attenuation on both pre- and postcontrast imaging. If the HU are greater than 10, contrast imaging with delayed imaging for washout evaluation can be performed. With this combined approach, Caoili et al. report a sensitivity and specificity for characterizing an adrenal mass as an adenoma as opposed to a nonadenoma of 98% and 92%, respectively (232). FDG PET should at least be used with inconclusive evidence in a patient with a known malignancy (225).

PET can be useful to differentiate benign from malignant adrenal masses, especially when there are indeterminate adrenal lesions on CT in a patient with otherwise operable NSCLC. The noninvasive characterization of adrenal masses using PET may decrease the number of biopsies and reduce the risk of surgical complications. In two studies, the sensitivity of FDG PET for detecting adrenal metastasis was 100%, and the specificity ranged from 80% to 100% (233,234). In the largest study published by Kumar et al., comparing uptake in adrenal lesions with background liver activity in 94 patients with lung cancer, the authors found an overall sensitivity of 93% and specificity of 90% (235) (Fig. 37).

Combined PET/CT improves the performance of FDG PET alone in discriminating benign from malignant adrenal lesions in oncology patients. In one study of 175 adrenal masses in 150 patients, using a SUVmax cutoff of 3.1, PET data alone yielded a sensitivity, specificity, and accuracy of 99%, 92%, and 94%, respectively, while combined PET/CT data yielded corresponding values of 100%, 98%, and 99%. Moreover, specificity was significantly higher for PET/CT ($P < 0.01$). The performance of PET/CT in detection of lesions of smaller size was assessed as well in this study. Fifty-one of the 175 masses were 1.5 cm or less in diameter. When a cutoff SUV of 3.1 was used for these smaller lesions, 18F-FDG PET/CT correctly classified all lesions (236). Recently, Caoili et al. found that adrenal

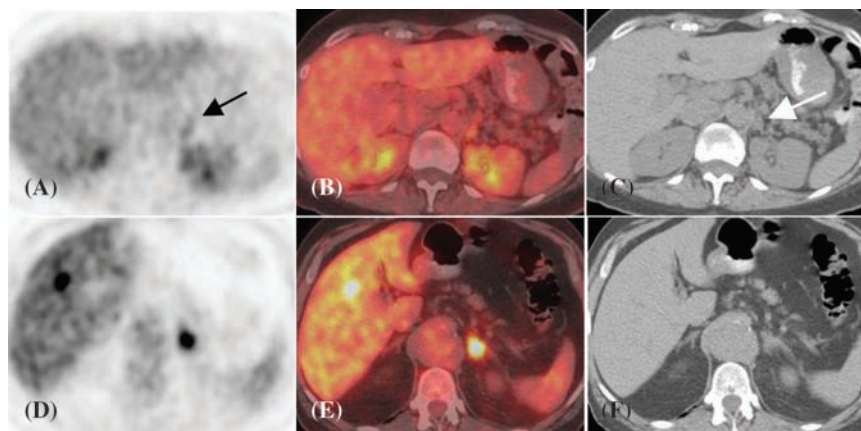


Figure 37 Patient underwent a PET/CT for staging of lung cancer. (A) FDG PET shows mild (SUV 2.7) uptake (arrow) fusing (B) to the left adrenal gland (arrow), which on CT (C) shows a small nodule and is low density (albeit not <10 HU on region of interest analysis, probably due to partial volume effects). Over a six-month period the gland remained unchanged on CT and PET and was consistent with an adenoma. (D–F). Another patient with a newly diagnosed lung cancer in whom a metabolically active left adrenal metastasis on PET (D) is seen fusing (E) to an enlarged gland on CT (F). A metabolically active liver metastasis is also seen without significant CT findings.

mass uptake that visually was less than liver was more specific for an adenoma while activity that exceeded liver was more specific for neoplasm (237).

False-positive PET findings are encountered at integrated PET/CT in approximately 5% of adrenal lesions. Occasionally, functioning adrenal adenomas demonstrate positive FDG uptake at levels even higher than those in the liver (238). In addition, pheochromocytoma, adrenal cortical hyperplasia, and adrenal endothelial cyst have been reported to show increased FDG (239). Since false-positive results have been reported and given the limited data on characterization of small lesions (<1 cm), pathologic proof is still warranted in case where a management decision (e.g., curative vs. palliative treatment) is to be made on the basis of the adrenal gland finding.

False-negative findings on PET may be seen in adrenal metastatic lesions with hemorrhage or necrosis, small-sized (<10 mm) malignant nodules, and metastases from pulmonary BAC or carcinoid tumors (239).

Thus, when there is discordance between CT findings and FDG PET, when the mass exceeds 4 cm in diameter, or when masses are hyperfunctioning, biopsy or surgical management of the mass may be indicated (240).

Osseous metastases. Osseous metastatic disease in lung cancer typically affects the vertebra, ribs, and proximal aspects of the extremities (Fig. 39). Osseous metastases from lung carcinoma are commonly lytic areas containing soft tissue density within on CT. In the past, bone involvement by lung cancer was assessed more frequently with bone scintigraphy than with FDG PET,

since bone scintigraphy has good sensitivity albeit low specificity (198) (also see chapter on bone metastases).

In a study of 110 patients with NSCLC, 18F-FDG PET was compared with bone scans for the evaluation of bone metastases (241). PET was reported to have a similar sensitivity ($\geq 90\%$), but a higher specificity ($\geq 98\%$) and accuracy ($\geq 96\%$). With regard to lung cancer, another more recent review of the literature concluded that 18F-FDG PET sensitivity was similar to that of bone scintigraphy, although PET specificity was higher than that of bone scintigraphy (242). Different patterns of uptake have been described in relation to the morphology of the lesion: lytic, sclerotic, or mixed (242). In lung cancer, the different CT and FDG uptake patterns may indicate different stages of the same process. For example, a lytic appearance on CT that is strongly FDG-avid (Fig. 38) may be one of the earliest signs of a metastasis while a sclerotic lesion lacking FDG uptake may indicate a “burned out” or healed metastasis (Fig. 39).

Given these studies support the superiority of FDG PET to bone scintigraphy in the detection of bone involvement, PET is likely to supplant bone scintigraphy in clinical practice. However, the practical advantage of 18F-FDG PET or PET/CT over bone scintigraphy remains somewhat controversial. The argument has been made that bone scintigraphy images the entire skeleton, a standard FDG PET images from the head to just below the pelvis, and thus could miss metastases in the skull and lower extremities. Part of the problem may be obviated given that a cranial CT or MRI is needed to evaluate for brain

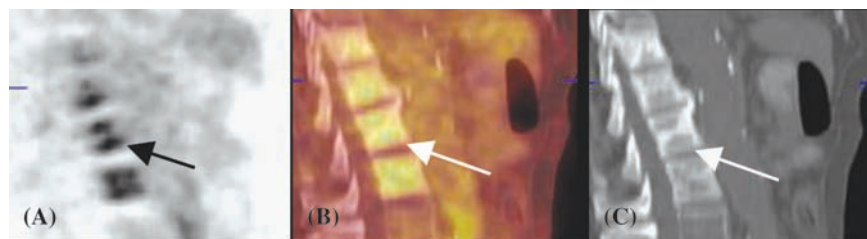


Figure 38 A 60-year-old man with a history of lung. Sagittal PET (A), fused PET/CT (B) and CT (C) views showing active metastatic lesions corresponding to lytic areas (arrows) seen on CT views. The sclerotic areas show less intense activity and are consistent with burnout metastasis.

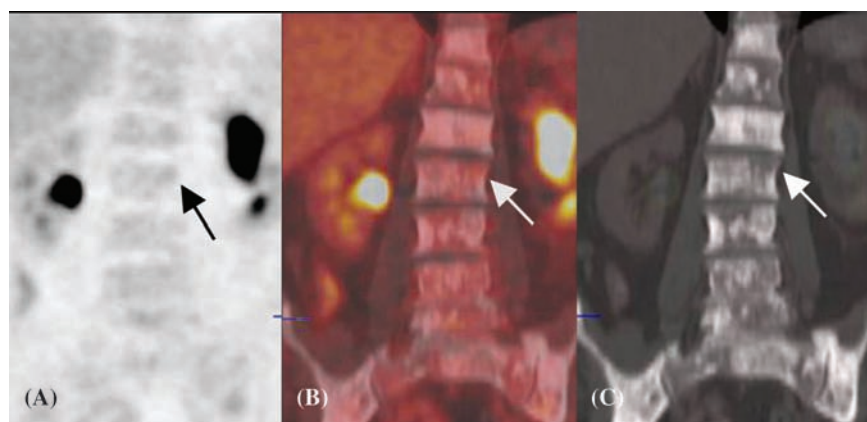


Figure 39 Coronal PET (A), fused PET/CT (B), and CT (C) views. An example of “burned-out” sclerotic metastasis in a patient with non-small cell lung cancer after chemotherapy. Minimal activity remains in some lytic areas (arrows).

metastasis. The frequency of missed bone metastases in the lower legs, if a staging work up entails FDG PET/CT alone, is unknown.

Brain metastases. FDG PET is not ideally suited for the detection of brain metastases in a patient with NSCLC and SCLC given its reported sensitivity is low (60%) (243). FDG PET has shown to contribute little in terms of imaging the brain and skull, as only 0.4% of 1,026 patients with multiple different malignancies had unsuspected cerebral or skull metastases (244). Reasons for false-negative PET scans are the high normally cortical FDG uptake and the limited spatial resolution of the PET scanners. Therefore, contrast-enhanced cranial CT and/or MRI remain the method of choice to stage the brain.

Liver metastases. The evaluation of liver metastasis from NSCLCa by PET is less well studied (Fig. 37D–F). There are no studies on the use of PET in patients with solitary liver metastases from NSCLC. In studies on staging distant disease in NSCLCa, some data suggest that PET is more accurate than CT (234) and that PET combined with CT provides additional diagnostic information in the differentiation of hepatic lesions that are indeterminate on conventional imaging (245). Nonetheless, current practice dictates the use of clinical evaluation first

followed by other modalities (198). CT and/or ultrasound with a sensitivity of 90% to 94% for metastases from NSCLCa remain the standard imaging techniques for the liver (198). Liver metastases appear as hypoattenuating soft tissue masses on unenhanced CT.

Stage designation and subsequent clinical management

Staging plays an integral role in developing clinical plans for patient management. A recent review of the literature shows that the use of PET imaging (either alone or in combined PET/CT technique) has a substantial impact on patient’s staging. Twenty-seven to sixty-two percent of the patients with NSCLC had their stage changed when PET was added to the conventional process. Patients were more frequently upstaged, mainly due to the detection of unexpected distant lesions by PET. As a consequence of more accurate staging, patient management was also altered in 25% to 52% of the cases (243).

The treatment of patients with lung cancer is complex, requires a multidisciplinary approach, and varies according to a number of clinical factors, including patient comorbidities. In general, curative intent therapy for lung cancer typically entails chemotherapy, radiation

with or without surgery. Surgery is typically performed for tumors shown to be associated with improved survival and cure. These include early stage disease stages I and II and potentially IIIA. Induction, or neoadjuvant, chemotherapy and potentially radiotherapy can be administered to downstage or decrease the tumor burden patients, such as those with stage IIIA disease. After induction chemotherapy and potentially radiotherapy is given, restaging is performed typically with CT, although PET/CT imaging has increased. After induction chemotherapy, N2 nodes in IIIA patients with tumors that fail to respond are associated with poorer prognoses and therefore not good candidates for surgical resection (246).

Patients with resectable NSCLCa may receive adjuvant chemotherapy after removal of the primary tumor. Data support a role of adjuvant chemotherapy for stage IIIA, II and IB, although a large number of factors contribute to the decision to pursue this (247). The overall benefit of adjuvant chemotherapy in stage IA is unclear at this point (247). In terms of radiation therapy and early stage disease, stage I and II disease in patients who are medically inoperable can be treated with only radiation therapy. Radiation and chemotherapy are administered together for typically bulky advanced-stage tumors (248).

Treatment for stage IIIB or locally advanced lung cancer typically entails concomitant cis-platinum-based chemotherapy and radiation for curative intent (249). Stage IIIB includes tumors that have invaded vital structures that cannot be resected (T4) or are associated with a malignant pleural or pericardial effusion or satellite nodule within the same lobe. Any contralateral mediastinal or hilar lymphadenopathy or distant metastatic disease places individuals with lung cancer into these categories.

Stage IV patients with oligometastatic disease or a solitary brain or adrenal metastases can be treated for curative intent. The remaining patients with stage IV disease along with individuals with locally advanced stage IIIB who cannot receive treatment for curative intent due to comorbidities and tumor factors receive palliative treatment. Palliative therapy for advanced disease typically includes cis-platinum-based chemotherapy and radiation therapy.

Considerations pertaining to NSCLCa staging system

Despite the revisions in the International Lung Cancer Staging System, patients with tumors of varying biological behavior and prognosis are grouped together within the same stage grouping. Stage IIIB remains a heterogeneous group of patients ranging from those with malignant pleural effusion to those with contralateral adenopathy. Additional varying degrees of ipsilateral mediastinal node metastases are grouped within stage IIIA. For example, patients with bulky mediastinal disease are different than those with micrometastatic nodal involvement found only

by surgical nodal sampling (192). Tumor extension outside the confines of the lymph node, or extranodal extension, also has strong negative prognostic implications particularly for stage II and III disease, which is currently not included in the staging system (250).

In terms of the primary tumor, T4 satellite nodules are difficult to differentiate by imaging alone from incidental nodules in the same lobe or intraparenchymal lymph nodes (251). Additional questions pertain to the management of solitary small subsolid cancers, as these nodules may have differing prognosis as compared with other stage IA tumors. Finally, histopathological findings such as lymphatic and vascular invasion with a primary tumor and molecular techniques may help differentiate and stratify tumors in terms of prognosis and are not currently accounted for in the staging system.

Small Cell Lung Cancer Staging

SCLC is a neuroendocrine tumor with an aggressive growth pattern that commonly leads to early widespread metastases. More than 70% of SCLC is metastatic at the time of diagnosis (252). Patients often present with bulky hilar and mediastinal lymph node metastases with encasement of mediastinal structures and tracheobronchial compression. SCLCa is typically staged using the Veterans Administration Lung Cancer Study Group classification as limited or extensive disease (252). Limited disease implies disease that can be encompassed by a single radiation port. Tumor is isolated to one hemithorax and one-half of the mediastinum, and lacks an accompanying malignant pleural effusion. Disease extent is analogous to that seen in stage I to IIIA disease in NSCLCa (169,253). Controversy pertains to classification of ipsilateral and supraclavicular adenopathy and contralateral left hilar adenopathy in SCLCa staging. Extensive disease is any involvement beyond the boundaries of limited disease and includes a malignant pleural effusion (252,254). Treatment for extensive disease comprises chemotherapy, while patients with limited disease receive a combination chemotherapy and radiation (255).

Staging procedures for SCLCa can include CT of the thorax, bone scan, abdominal CT or MRI, head CT or MRI, and bone marrow aspirates (252). Mediastinoscopy is not required for staging SCLC. 18F-FDG PET's role in the staging of SCLC is controversial. FDG PET has been shown to improve management of SCLC in 8.3% to 29% of cases (256–259). Blum et al. (256) reviewed 36 consecutive SCLC patients for either staging, restaging after therapy, or both. In this study, 33% of patients who had PET for staging were upstaged from limited to extensive disease, while 63% of patients in whom PET was performed for restaging had discordant results with conventional imaging. The PET results impacted the management of 43% of cases. Changes to management included

modification of radiation fields, substitution of radiotherapy for chemotherapy because of increased documented disease, inclusion/exclusion of prophylactic cranial irradiation, and omission of further treatment because of an absence of detectable disease.

A prospective study by Brink et al. (258) investigated the performance of FDG PET in the primary staging of 120 consecutive patients with newly detected SCLC. Sensitivity of FDG PET was significantly superior to that of CT in the detection of extrathoracic lymph node involvement (100% vs. 70%, specificity 98% vs. 94%) and distant metastases except to the brain (98% vs. 83%, specificity 92% vs. 79%). Inclusion of FDG PET in SCLC staging resulted in correct stage migration in 11% of the patients. FDG PET correctly upstaged 10 patients to extensive disease and downstaged three patients by not confirming metastases of the adrenal glands suspected on the basis of CT. Only one patient was incorrectly staged by PET, where PET failed to detect brain metastases in the absence of further cancer spread. The stage migration led to significant changes in the treatment protocol of all affected patients.

PET, CT, and Lung Cancer Prognosis

Studies have shown the relationship of FDG uptake to proliferation in tumors and a relationship between SUV and clinical outcome (260). With the advent of integrated PET/CT systems and the possibility to perform dynamic contrast-enhancement CT studies, the relationship between blood perfusion and glucose metabolism of lung nodules/masses has been the subject of investigations (122,261). Tumor flow–metabolic relationships could potentially be assessed by combining FDG PET and contrast enhanced CT (CE-CT) in a single examination providing a better characterization of the biological features of a tumor than either method alone. Quantitative CE-CT may characterize pulmonary nodules on the basis that angiogenesis within malignant nodules will be depicted as increased perfusion (121,262). It has been showed that measurements of contrast enhancement of lung tumors correlate with microvessel density and with expression of vascular endothelial growth factor (263–265).

However, previous studies evaluating the relationship between blood flow and glucose metabolism in lung tumors have yielded variable results, with reports of statistically significant correlations between tumor glucose metabolism and perfusion imaging (266) and studies showing no such correlation in stage IIIA, N2 NSCLC, or in pulmonary metastases (267,268). In addition, treatment targeting the tumor vasculature causes variable changes in glucose metabolism and blood flow (269–272). This suggests that blood flow and metabolism may be coupled in early resectable NSCLC but become uncoupled in

larger lesions, in the later stages of disease, and following therapy when glucose metabolism is stimulated by hypoxia and when the tumor blood flow is impaired (273,274). Recent work from Miles et al. (261) confirmed that the relationship between tumor blood flow and glucose metabolism in NSCLC is dependent upon tumor size, with the greatest metabolic flow differences found in larger tumors of higher stage. This variability in the relationship between blood flow and metabolism indicates that FDG PET and quantitative CE-CT cannot be considered equivalent markers of malignancy. The finding of low perfusion in large tumors highlights an important pitfall for quantitative CE-CT in the diagnostic assessment of pulmonary nodules, particularly for nodules with a diameter greater than approximately 2.5 cm.

PET and Radiation Treatment Planning in NSCLC

PET/CT imaging is being increasingly used in setting up radiation therapy treatment for lung cancer (248,275). This has been accomplished by integrating PET data with planning CT data manually or semiautomatically or by using PET/CT for planning. Several issues arise in using PET data for this purpose. Some are technical, most often related to the optimal method for defining the volume of metabolic tumor (276) and for dealing with respiratory motion. Although methods to define treatment volumes using a threshold of 40% of maximum tumor SUV have been investigated most commonly, thresholds of 15% to 20% of maximum tumor SUV or set levels of SUV (at 2.5) have correlated somewhat better with gross tumor volumes as defined by CT (276,277). Nonetheless, the proper SUV threshold appears to change relative to overall size of the tumor and no one technique for defining the “metabolic” treatment volume has yet to be validated (277). Respiratory motion contributes to the uncertainty when integrating metabolic information from PET/CT (278). PET volumes may be determined by incorporating the location of the tumor throughout the entire respiratory cycle (278) or by performing respiratory gating in which a particular portion of the respiratory cycle is used (279,280).

Radiation planning using PET and CT information performed on an integrated PET/CT has resulted generally in changes in treatment volumes (281), some reduced in size and some increased (282–284). There is a clear advantage in incorporating PET from PET/CT into planning since PET helps distinguish atelectasis from tumor (Fig. 40) (285) and will result in a reduced treatment volume compared with CT-based plans alone in that setting. Controversy has developed around the idea of excluding atelectatic and metabolically inactive lung, since it is not known how often or to what extent tumor infiltration into atelectatic lung occurs (278). Also, the

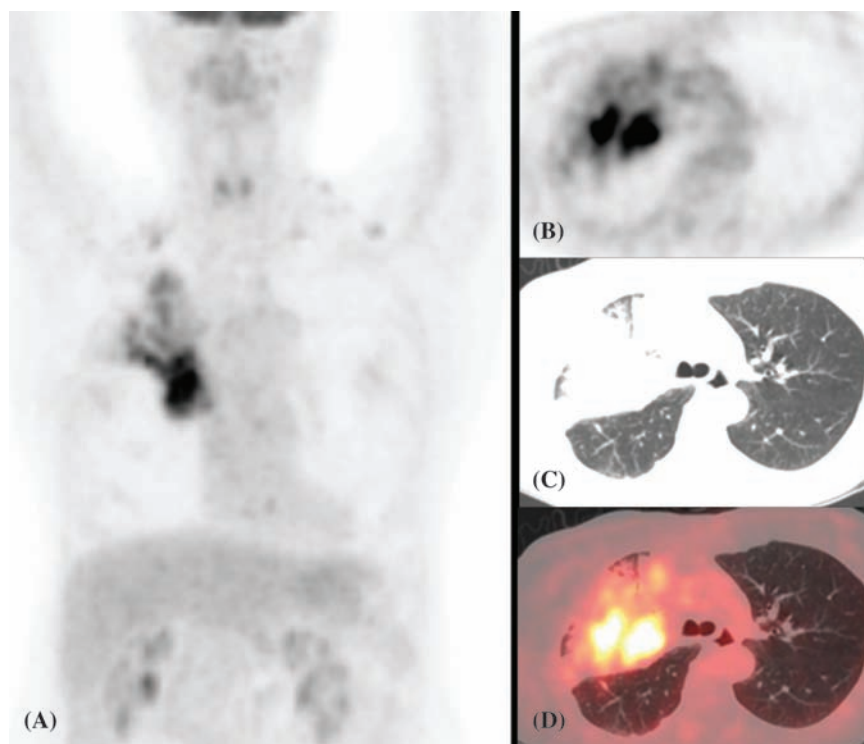


Figure 40 Utility of PET for delineating tumor from surrounding atelectasis. Seventy-three-year-old man who presented with fever and cough. CT scan revealed atelectasis and consolidation in the right upper lobe. Bronchoscopy was positive for a non-small cell lung cancer. A PET/CT was performed for staging. (A) Anterior MIP view shows the central metabolically active tumor at the right hilum as well as a separate focus in the right upper lobe. Less intense uptake is seen peripherally. This is again appreciated on the transaxial PET slice (B). A large area of increased density is present on the CT (C) lung windows. The fusion image (D) shows that the tumor occupies only a portion of the CT density. The less intense activity was felt to represent post obstructive pneumonitis in the atelectatic lung. It is not certain whether there was microscopic infiltration of tumor into the atelectatic portions. *Abbreviation:* MIP, maximal intensity projection.

sensitivity of FDG PET for nodal involvement will result in alterations in the shape of the radiation field in 22% to 62% (286,287). Lastly, the integration of FDG PET information from an inline PET/CT has been shown to diminish interobserver and intraobserver variation in treatment plans (288–290). Overall, the consensus appears to be that the incorporation of FDG PET may decrease dose to normal tissues and permit more thorough incorporation of tumor into treatment fields, but outcomes data is not yet available (291).

PET/CT for Restaging and Identifying Recurrent Disease

The difficulties pertaining to initial staging and noninvasive imaging also apply to restaging; yet, a precise assessment of response is necessary for optimal patient management. Early detection of a relapse has become important in the follow-up of patients after initial treatment since new salvage therapies are now available.

Restaging is typically performed noninvasively. The criteria for conventional restaging are mainly based on changes in tumor size. The WHO definitions have been the criteria most commonly used by investigators (292). The criteria have been modified by the National Cancer Institute and the European Association for Research and Treatment of Cancer and published in the *Journal of the National Cancer Institute* in 2000 termed the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. (293).

Tumor response is defined as a therapy-induced reduction of the largest dimension of the tumor by 30% (293). Morphologic responses to therapy usually occur over several weeks to months and change in tumor volume may be obscured by scar tissue formation, inflammation, and edema.

FDG PET/CT is able to assess and quantify tumor glucose uptake, which is related to cell proliferation and growth, and thus can aid in the assessment of response to therapy and the presence of residual viable tumor. The

experience with PET in determination of metabolic response to therapy is still limited and can be grouped in three clinical scenarios: restaging after neoadjuvant therapy, early assessment of response to therapy, and restaging after completion of therapy. Furthermore an understanding of the specific changes incurred after surgery or radiotherapy on both CT and PET is critical.

Restaging After Neoadjuvant Chemotherapy

A number of series have focused on restaging locally advanced NSCLC with PET after induction chemotherapy or chemoradiation to identify patients who would benefit from tumor resection (294–297). For determining viability of the primary tumor with PET after induction chemotherapy, a sensitivity of 94.5%, specificity of 80%, and overall accuracy of 91% was recently reported (298). In these studies, the accuracy of PET in determining mediastinal lymph node involvement after therapy varies (210–212). In assessing mediastinal “downstaging,” an accuracy of 100%, compared with 67% for CT was first reported (299), but later studies have demonstrated less optimistic results with a sensitivity as low as 58% (300). For mediastinal restaging, other reported sensitivities are between 67% and 88% and specificities between 61% and 93% (294,298,300). The accuracy of PET is not as high for restaging after induction therapy as with initial staging, with particular low sensitivities reported for hilar lymph nodes (15%), although PET performed better than CT with higher positive predictive and negative predictive values (295). Postinduction decreases in SUV by 80% have a significant prognostic value for patients (298,301). Also, postinduction metabolic changes in the primary tumor and mediastinal lymph nodes appear to have greater prognostic significance compared with change in size on CT alone (301).

Early Assessment of Response to Therapy

Metabolic information from PET/CT has been shown to reflect response to therapy earlier than morphological changes on CT. Such metabolic data may prove important for restaging patients while therapy is ongoing by perhaps predicting those that may not respond to therapeutic measures and hence enabling an earlier change of therapeutic course. However, this will need further validation at this point (302). A study by Weber et al. revealed that after one cycle of chemotherapy for stage IIIB disease, metabolic responders, those with a decrease in tumor SUV more than 20%, or two standard deviations of the usual variation in tumor glucose uptake, more frequently showed a standard response to therapy after full treatment and had a significantly longer median time to progression and overall survival (303,304). A poor response after one cycle predicted disease progression within the first three cycles of chemo-

therapy (303). On the other hand, less accurate prognostic stratification is obtained by conventional imaging (305). In a limited experience with PET in radiofrequency ablation, increasing SUV two months after therapy was associated with progression at six months or longer from therapy. A decrease at two months predicted response (307).

Restaging After Completion of Therapy

CT is widely used for restaging after surgical, chemotherapy, and radiation therapy. Adding 18F-FDG PET to the posttreatment restaging also provides important prognostic information that can augment the pre treatment prognostic assessment (Fig. 41). Patients with positive 18F-FDG PET results posttherapy have a significantly worse prognosis than patients with negative results, predicting shorter survival (305). Furthermore, results of posttherapy 18F-FDG PET have a significant impact on further management, with major changes in management plans occurring in 63% of studied cases (306).

Normal Postsurgical PET/CT Appearance

An understanding of the postsurgical appearance after lung resection is important for the identification of surgical complications and recurrent tumor. Given the wide range of normal findings and complications that can occur, this section will focus on the more common findings after surgery, and a detailed description of the postoperative complications will not be covered.

For chest CT evaluation in the post-lung resection population, the administration of intravenous contrast during imaging is beneficial for assessing the hilar structures, which are frequently distorted on the side of removed lung. PET is more reliable in assessing disease activity when performed six months after surgery (308). When assessing the postsurgical thorax on PET or CT imaging, reference to any prior studies performed after surgery is helpful for confirming a lack of change.

The lobe that has been removed is identified by review of the bronchial anatomy for missing bronchi on CT images. Shift of the remaining lung and mediastinal structures is also evident. After lobectomy, the hilum typically shifts toward the region previously occupied by the lobe, with accompanying shift of the mediastinum to the side of resection. Typically, after removal of the right upper lobe, the right middle lobe shifts superiorly and anteriorly to fill the space previously occupied by the right upper lobe while the right lower lobe is located posteriorly. After a right lower lobe resection, the right middle lobe often shifts to a more posterior location. Given that only one lobe is present on the left, the remaining lobe fills the entire left hemithorax after lobectomy. Removal of a portion of a lobe leads to

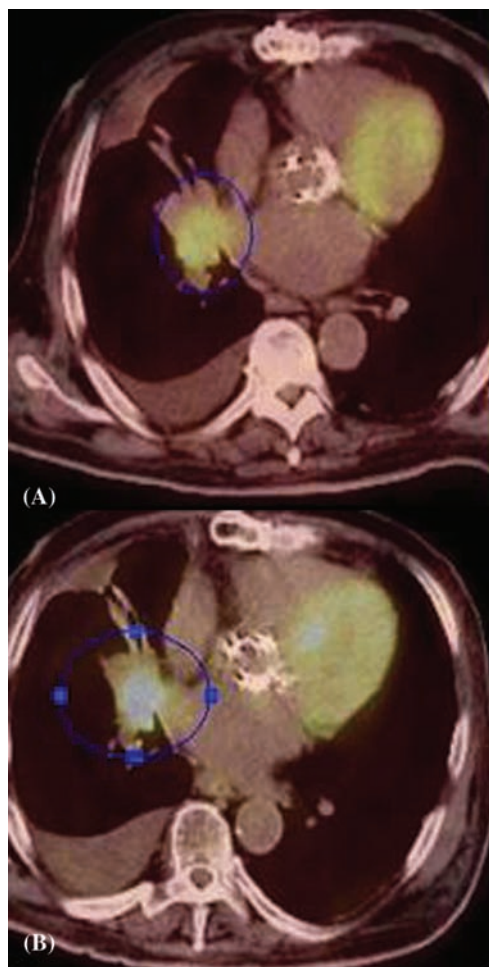


Figure 41 (A) Fused transaxial PET and CT performed in an 81-year-old man with a right hilar mass (SUVmax 7.1) on prechemotherapy scan. (B) The follow-up PET/CT after chemo and radiation therapy was acquired two months later. The right hilar mass demonstrated an interval increase in metabolic activity (to SUV max 8.8), although there has been no clear-cut increase in the size of the right hilar lesion on CT. There was also interval growth of a left adrenal gland (not shown) with a concomitant increase in SUV over that period of time. These findings were all compatible with progression through treatment. *Abbreviation:* SUV, standardized uptake value.

visualized consolidation and hemorrhage in the remaining lobe during the early postoperative period that resorb or evolve into areas of scarring with more linear, yet sometimes very focal, configuration. High attenuation suture material or staples may be present in close vicinity. Soft tissue areas in the hilar regions and in the lung parenchyma gradually decrease over time. FDG PET in the postoperative patient may show residual activity at the surgical stump after lobectomy, or along the line of resection early on. By four weeks after surgery, this is

expected to be relatively low level and less than the chest wall wound.

Fluid collections in the pleural space may persist after surgery for variable lengths of time with ultimately only residual pleural thickening identified on the side of the thoracotomy. Enhancement of the pleural space should raise concern for an empyema or recurrent tumor. Pleural air or pneumothorax also occurs frequently in the early postsurgical period. The air in the pleural space can be seen up to one week after lobectomy and longer for pneumonectomies. After pneumonectomy, the entire lung has been removed, and therefore the initially air filled space becomes gradually obliterated as the mediastinal structures shift toward the pneumonectomy side with concurrent opacification of the cavity by fluid (309,310). If a pneumothorax persists longer than typical, the amount of air should be gradually decreasing, as assessed by review of chest radiography and other imaging. Otherwise a bronchopleural fistula or other cause of pneumothorax would be suspected. Bronchopleural fistulas are typically related to breakdown of the bronchial stump and occur early after surgery or are delayed. Bronchopleural fistulas have been reported in 2% to 13% of lung resection cases and are direct communications of a bronchus with the pleural space (310). When present, they are invariably associated with empyema. The delayed bronchopleural fistula should raise concern for recurrent tumor leading to infection. Any increase in the amount of soft tissue and nodularity in the pleural space raises question of tumor recurrence or infection.

Uptake at the thoracotomy site is also expected, and focal uptake in the ribs may persist for several months (308). However, nodular uptake in the mediastinum should be viewed with suspicion on PET.

Radiation Therapy Changes

Radiation therapy creates the formation of free radicals that interact with DNA to induce damage (248). The delivery of radiation therapy for lung cancer treatment creates significant lung distortion and lung opacity, making the diagnosis of recurrent tumor difficult when using morphological assessment. Because of this, a greater role for PET/CT has been implicated.

Symptomatic radiation pneumonitis occurs most frequently between 6 and 13 weeks after the completion of radiotherapy (311). Typically, acute radiation injury becomes evident on CT approximately four weeks to three months after finishing therapy (312,313). The injury appears first as diffuse homogenous or discrete ground-glass opacities that progress toward consolidation. These acute radiation changes regress with development of fibrotic areas,

typically begining approximately 6–12 months after completion of radiation therapy. (Fig. 3) The fibrotic change manifests as traction bronchiolectasis, architectural distortion, reticular opacity, atelectasis, and consolidation. The fibrotic changes can progress for up to two years prior to stability (312–315). Increasing volume loss occurs in areas of lung that are irradiated. The extent and shape of the radiation changes depend upon the size of the radiation port. The primary tumor typically decreases in size on CT with radiation treatment, while injury in the surrounding lung develops. An area without air bronchograms within the radiation pneumonitis is suggestive of residual or persistent tumor. Radiation pneumonitis in a paramedastinal distribution occurs with radiation therapy for mediastinal and hilar nodal disease. Tumor in the mediastinum after irradiation decreases in size, however, may never completely resolve on CT.

More precise delivery of radiation to a structure of interest is enabled by three-dimensional conformal radiation therapy (CRT). CRT entails shaping of the beam to spare normal areas (248,316). Intensity modulated radiation therapy (IMRT) technique is a specialized form of CRT that further decreases radiation injury by sparing surrounding normal tissue while improving treatment to the tumor (317). IMRT involves splitting of the radiation beam into higher and lower intensity areas to maximize radiation delivery to the tumor center while minimizing the dose directed towards the tumor margins and surrounding structures (248,317,318). With CRT, focal radiation pneumonitis, surrounds the small immediate area around the tumor within three months of treatment completion (318) Koenig et al. classified patterns of fibrosis as modified conventional, mass-like, and sac-like. Modified conventional fibrosis involved less extensive consolidation, volume loss, and bronchiectasis than radiation fibrosis from conventional therapy and occurred in 5 of 19 patients. Mass-like fibrosis occurred in eight patients and was defined as traction bronchiectasis and focal consolidation at the site of the tumor. Scar-like fibrosis, or linear opacity in the vicinity of the tumor with accompanying moderate to severe volume loss, was reported in six cases (318). Percutaneous image-guided radiofrequency ablation is occasionally used for unresectable disease or metastatic tumors. The procedure entails placement of a radiotherapy wire directly into the tumor via an introducer needle placed transcutaneously (319).

An understanding of the normal PET behavior after radiation therapy is needed. Early signs of local tumor relapse are difficult to identify in areas with therapy-induced fibrosis on CT. PET/CT is useful for identifying the presence of residual and recurrent tumor in the mediastinum and lung parenchyma (Fig. 42) (320). False-positive studies may occur if PET is performed shortly after radiotherapy or surgery. Usually this uptake

is more diffuse and conforms to the shape of the radiation port (320). The intensity of FDG activity cannot be used as a criterion since uptake in areas of pneumonitis frequently exceeds the level that might ordinarily be consistent with malignancy ($SUV > 2.5$) (320). In a series of 73 patients examined at a median 70 days after radiotherapy, PET/CT, the intensity of uptake of the surrounding soon after completion of chemoradiation or radiation alone showed a significant correlation with metabolic tumor response (320). As described above, uncomplicated acute postradiotherapy inflammatory CT changes decline to a minimum after three to six months. Therefore, a time interval between initiation of treatment and follow-up PET scan of at least three months is recommended to increase PET accuracy (306). However, in our experience, activity may persist for many months after the completion of therapy.

PET and PET/CT for Tumor Recurrence

Even in stage I NSCLCa patients treated with surgery, the recurrence rate is as high as 20% (321,322). Early detection of a relapse has become important in the follow-up of patients after initial treatment since new salvage therapies are available.

The negative predictive value of CT for tumor recurrence has been reported by Korst et al. to be high (99%); however, the positive predictive value was only 53%. In this study, the CT findings of recurrent cancer included enlarging or greater than 1 cm pulmonary nodules and pleural effusions that developed more than one year after surgery (323). When a suspicious abnormality is detected on conventional restaging, PET/CT is frequently used to assess these abnormalities (Fig. 42). The addition of PET to the assessment of the suspected recurrence may lead to a change in management (308).

Recurrence in the lung in a postsurgical patient is suspected when hilar soft tissue increases on CT. The hilar or stump regions are the most common sites of recurrence in postsurgical patients (324) (Fig. 43). As mentioned previously, a delayed new pneumothorax in a post-lung resection patient raises suspicion for a bronchopleural fistula related to hilar recurrence or infection. Infection of the pleural cavity can result from a bronchopleural fistula. In the setting of new or worsening pleural thickening with or without pneumothorax, FDG PET can be especially helpful in identifying recurrence (308). More recently, Hellwig et al. in a series of 73 patients treated with surgery and with suspected tumor recurrence reported FDG PET alone to have a sensitivity of 93%, specificity of 89%, and accuracy of 92% for tumor recurrence. Postsurgical change without tumor showed a significantly lower SUV. Furthermore, for those cases treated with subsequent surgery for tumor, patients with tumors

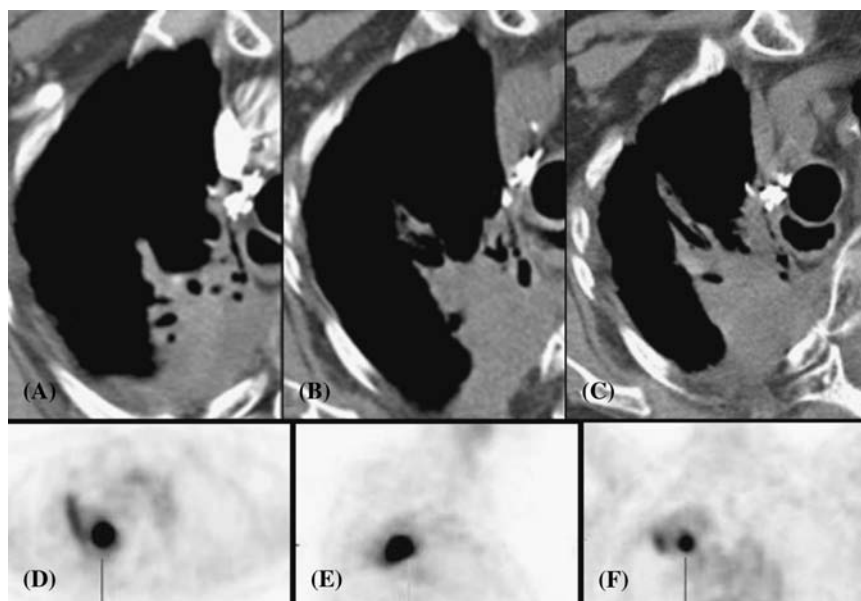


Figure 42 A 67-year-old woman who completed radiation therapy in 2005. (A) CT scan performed shortly after the completion of therapy in 2005 shows radiation change in the right lung. (B) CT performed in 2006 at the same transaxial level shows change felt to represent further retraction and healing over the interval. (C) CT performed as part of the PET/CT in 2007 shows subtle increase in soft tissue. Transaxial (D), sagittal (E), and coronal (F) PET images from the 2007 PET/CT show focally intense (SUVmax 13.4) uptake corresponding to the right upper lobe soft tissue. Biopsy showed a recurrence. *Abbreviation:* SUV, standardized uptake value.

having high SUVs (>11) had a poorer prognosis and shorter survival overall (325).

After radiation therapy, lung cancer recurrence should be suspected when there is enlargement, change in shape, or attenuation of any residual density in the region of the primary tumor (Fig. 42). A loss of the air bronchograms within an area of radiation pneumonitis is also suspicious for recurrent tumor. CT imaging can miss early signs of relapse in areas with therapy-induced fibrosis. Several studies have focused on the use of PET in the characterization of viable tumor and scar tissue after therapy (326). PET is able to correctly confirm or exclude disease relapse in an indeterminate lesion on CT scan with a sensitivity of 97% to 100%, specificity of 62% to 100%, and accuracy of 78% to 98% (306,327).

Compared with initial staging, the specificity of PET alone is less for patients who have been previously treated with radiation and surgery because of posttherapy complications with inflammatory components. However, with PET/CT, evaluation of the CT attenuation correction images along with the metabolic PET information may help distinguish between inflammatory change and recurrent tumor (328). In a series of 42 patients with suspected tumor recurrence, PET/CT and interpretation of PET data alone were compared in terms of specificity. Specificity was shown to improve from 53% for interpretation of PET

alone to 82% for PET/CT, with a positive predictive value of 75% for PET alone that increased to 89% for PET/CT (329). Clearly, PET/CT plays an important management role in patients with an area of suspected local recurrence on conventional imaging or even when tumor markers or symptoms suggest recurrence.

Tumor recurrence in the mediastinum presents as enlarging adenopathy. Kelsey et al. reported in 61 postsurgical patients that recurrence in the mediastinum occurred with equal frequency in those patients who originally had N0 disease and those who had initially presented with N1 or N2 disease. However, patients with previous N1 or N2 disease had a higher frequency of lymphadenopathy in the supraclavicular region compared with those individuals who originally had N0 disease (324). Although conventional imaging and FDG PET may be used routinely, occasionally patients will present with paraneoplastic syndromes at the time of recurrence (330). In that setting, PET/CT is useful to localize the recurrence.

Confirmed Secondary Lung Malignancy

Metastatic disease can involve any of the thoracic structures, including the lung parenchyma. Secondary lung malignancy originates from another intrathoracic neoplasm, such as a lung carcinoma, breast cancer, or

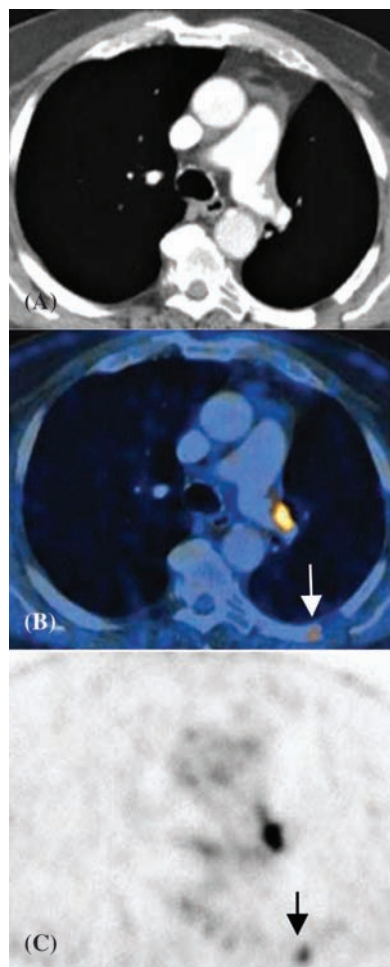


Figure 43 Patient status post left upper lobe resection for lung cancer. On a follow-up diagnostic CT an area of slightly increased soft tissue was questioned in the left hilum. CT (A) from a PET/CT performed for further evaluation shows minimal soft tissue in the left hilum that is difficult to differentiate from postsurgical changes. Fused (B) and PET alone (C) images at this level show the uptake in the left hilum with SUV of 4.5 secondary to tumor recurrence. Also note persistent uptake in rib at the thoracotomy site (arrows). *Abbreviation:* SUV, standardized uptake value.

mediastinal tumor, or very frequently extrathoracic tumors, particularly from the gastrointestinal, genitourinary system, melanoma, and sarcoma. As opposed to a primary lung cancer, a dominant nodule or mass in the lung is often not present. Often secondary malignancy to the lung is accompanied by multifocal adenopathy in the mediastinum and hilar regions given the hematogenous dissemination and also the large role of lymph nodes in spread of cancer to the lung. The presence of any other intrathoracic abnormality, understandably, is helpful, as

the primary tumor may be present on the images, such as a breast or esophageal mass.

In the scenario of a newly presenting tumor in the thorax, the pattern of nodal disease accompanying the parenchymal findings may assist in the identification of the location of the primary tumor (22). Skip metastases, when nodes spared of malignancy intervene between an organ of the primary malignancy and nodes that are involved by malignancy can occur, however. Breast lymphatics drain into a subareolar plexus and then typically into the lower axillary nodes. Direct drainage into the axilla can bypass the subareolar plexus. The axilla also drains the corresponding upper extremity, and therefore adenopathy particularly localized to one side raises question of malignancies originating from the breast, upper extremity such as melanoma, or lymphoma. The presence of upper abdominal nodes and nodes adjacent to the esophagus may indicate an esophageal primary (22).

The spread of malignancy to the lung parenchyma can occur via the lymphatics, hematogenous pathways, and direct invasion. Lymphatic metastasis can arise from tumor spread initially to the lung via the blood stream with subsequent invasion of the vasculature and adjacent lymphatics. Alternatively, tumor can spread from the hilar regions into the peripheral lung parenchyma via the lymphatic pathways. Given that lymphatics are located in the periphery of the secondary pulmonary lobule and in the peribronchovascular interstitium, lymphangitic carcinomatosis manifests as reticular opacities, nodular or smooth, represented primarily by thickening of the interlobular septae accompanied by thickening of the central bronchovascular core within the lobule. Given that lymphangitic carcinomatosis can arise secondary to hematogenous spread to the interstitium, hilar, and lymphadenopathy is not a prerequisite. The lack of a pleural effusion does not exclude carcinomatosis.

Hematogenous dissemination of tumor to the lung results in multiple nodules, typically with well-circumscribed borders. Ground-glass borders in the setting of metastatic disease can be seen with malignancy that is hemorrhagic. Ground glass can be seen in tumors that have mucinous components such as pancreatic and colonic neoplasms (331). As mentioned previously, the attenuation of the metastatic disease may vary depending upon tumor type. Ossifying tumors and thyroid cancer may present with very dense nodules that can mimic granulomas when small. Other tumors may demonstrate calcification within metastatic deposits, such as gastrointestinal and genitourinary tumors. Liposarcomas, given their fatty attenuation, can present as fat-containing masses. Cavitation has been observed with squamous cell tumors. Lastly, direct invasion of the lung parenchyma by chest wall, pleural, and mediastinal masses leads to local disease initially.

BENIGN PARENCHYMAL DISEASE

This section deals with benign pulmonary entities that may be confused with malignant disease or that may coexist in patients with established diseases that are being evaluated with PET/CT. The PET findings in diffuse lung disease in particular have not been reported to any large extent, PET/CT findings have been described for some benign diseases and are also included for reference, although many of these descriptions have been limited to case reports or limited case series. While PET findings may be nonspecific, the CT findings of the more common causes of benign parenchymal diseases may be helpful for developing a basic differential diagnosis. It is beyond the scope of this text to provide an exhaustive review of all benign entities of the chest, and for a more in-depth description of these diseases, the reader is directed to established texts.

FDG PET in Inflammatory and Infectious Disease

It is well known that inflammatory cells show increased FDG uptake, but usually they have lower FDG-avidity when compared with malignant cells. In fact, using a threshold of SUV of 2.5 to 3.8, it is possible to separate malignant from many benign inflammatory lung nodules with high specificity (39). However, there is a considerable degree of variability in the FDG uptake among these nonmalignant causes. Certain chronic infectious processes, typically some granulomatous diseases, tend to reveal higher FDG uptake with semiquantitative values that overlap with those of malignant disorders.

Several factors may contribute to this phenomenon on a cellular basis. The metabolic trapping through phosphorylation of FDG to FDG-6-phosphate is the rate-determining step in retention of radiolabel in the cells. G6Pase is present at low concentrations in most cancer cells but tends to be overexpressed in inflammatory cells, diminishing the accumulation of radiolabeled glucose. The differences in the levels of G6Pase between tumor cells compared with inflammatory cells can, at least partially, explain differences in retention of FDG between malignant and benign cells. However, levels of G6Pase activity may also vary among different tumor cell types. Similarly, some inflammatory lesions may show a pattern of metabolic trapping of FDG similar to cancer cells (63).

In fact, glucose metabolic activity of inflammatory cells can increase dramatically (332). Similar to malignant cells, inflammatory cells also have increased expression of glucose transporters when they are activated. Moreover, multiple cytokines and growth factors are able to increase the affinity of glucose transporters to deoxyglucose (333–335). Other factors may contribute to

the degree of FDG uptake by inflammatory cells, such as the state of inflammation (acute vs. chronic), the type of inflammatory cells, and the combination of coexisting necrosis, hypoxia, and angiogenesis in the lesion (8).

Increased FDG activity has been observed in many benign infectious and/or inflammatory conditions (Table 13). These disorders can result in false-positive interpretation of FDG PET studies in patients presenting for the evaluation of lung cancer. On PET alone the findings are often nonspecific, but examination of the CT characteristics is helpful.

Although at this time PET does not appear to have a role in the initial diagnosis of inflammatory conditions, PET allows monitoring of the activity of inflammatory processes and for any response to therapy during the course of the disease given its ability to quantify FDG

Table 13 PET-positive infectious and inflammatory processes

Infectious processes (references)

- Bacterial pneumonia (517,518)
- Lung abscesses (519)
- Viral pneumonia (520)
- Pneumocystis Carinii infections (515,516)

Mycobacteria

- Mycobacterium avium-intracellulare* (340)
- Tuberculosis (336)

Fungal

- Actinomycosis (589)
- Histoplasmosis (42)
- Aspergillosis (42,337,338)
- Blastomycosis (519)
- Cryptococcosis (43)

Noninfectious inflammatory processes

- Granuloma (519)
- Wegener's disease (57)
- Plasma cell granuloma (590)
- Sarcoidosis (429–432,591)
- Rheumatoid arthritis with associated lung nodules (409,592,593)
- Idiopathic pulmonary fibrosis and usual interstitial pneumonitis (498,594,595)
- Amyloidosis (596)
- Asthma (597)
- Lipoid pneumonia (466,467)
- Barium aspiration (410)
- Drug-induced lung disease
 - Bleomycin-induced alveolitis (598)
 - Amiodarone (470)

Congenital diseases

- Cystic fibrosis (533,599)

Occupational

- Anthrassilicosis (410,600)

Vascular

- Pulmonary emboli, iatrogenic (452)
 - Pulmonary emboli (59,451,452)
 - Pulmonary infarcts (59,451)
-

uptake. This use has already been suggested for evaluating a variety of inflammatory diseases such as tuberculous spondylitis (336), aspergillosis (337,338), echinococcosis (339) and *M. avium-intracellulare* infection (340).

Focal Nodular or Mass-like Opacities

Focal nodular or mass-like opacities are very common findings that may lead to diagnostic confusion with malignant disease. A broad variety of benign entities may appear as nodular or mass-like lesions. Broadly these may be characterized as infectious, noninfectious inflammatory, vascular, or miscellaneous. Unfortunately, the CT appearances of these pathologies may closely mimic those of malignant lesions, and differentiation may require an evaluation of not only the CT morphology and associated PET activity but also consideration of the clinical setting. The duration of findings, rate of progression or regression, the timing, and nature of administered therapies including radiation therapy and the current immune status of the patient are but a few of the important factors in determining the nature of nodules or masses in the chest.

CT in Infection

Most commonly, infection appears as an area of parenchymal consolidation. However, occasionally parenchymal infection may manifest as a discrete nodule or mass. It is in these instances that differentiation from a malignant mass may be problematic (160,341). Indeed, an active infection or a postinfectious nodule is the likeliest cause of

a benign nodule that may mimic lung neoplasia. Larger nodular or mass-like areas of parenchymal infection are known to be relatively common in children, the so-called “round pneumonia,” and are widely acknowledged to occur in adults also (342). Such nodular densities can occur as an infection is developing or, more commonly, regressing. Radiological findings that suggest an infective etiology are the presence of intrinsic air-bronchograms or the presence of other areas of parenchymal consolidation or bronchiolitis. The latter may be observed near the periphery of larger nodules or mass-like areas of round pneumonia (343).

Although any bacterial infection may be the culprit of an infectious nodule, the presence of discrete nodules should raise the suspicion of fungal or mycobacterial disease (Fig. 44). In this context it is essential to be aware of the immune status of the patient. The presence of cavitation in infective nodules may be seen in fungal and mycobacterial disease but is also seen with bacterial septic emboli. Some of the commoner diseases that may result in infectious nodules are discussed below.

Mycobacterial disease

Mycobacterial disease may be caused by a wide variety of mycobacterial pathogens. Although classical tuberculosis is associated with *Mycobacterium tuberculosis*, increasingly many atypical mycobacteria are recognized as causes of chronic infection. The manifestations of mycobacterial disease will depend on the individual pathogen, the host immunity, the underlying pulmonary architecture, and the phase of infection.

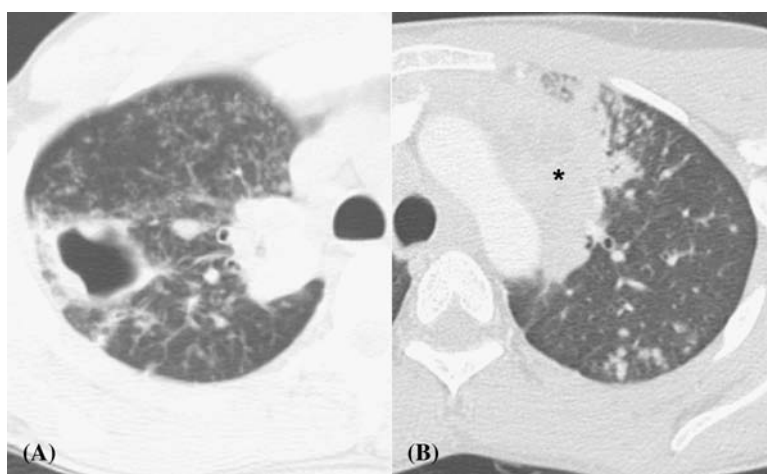


Figure 44 Two examples of reactivation tuberculosis. (A) A cavity is present in the right upper lobe. Multiple other clustered nodular densities are indicative of bronchiolitis and support an infective rather than neoplastic etiology for the cavity. (B) A confluent area of mass-like consolidation in the left upper lobe is present (asterisk). At the edges of the mass and peripherally in the posterior lung, areas of infectious bronchiolitis are also present. Both the larger mass and the areas of bronchiolitis are likely due to infection in the lung from tuberculosis.

Tuberculosis. Primary infection with tuberculosis occurs following inhalation of tubercle bacilli and is characterized by the formation of a focus of parenchymal infection called the Ghon focus. Spread may occur locally to the regional nodes. This phase of infection in immunocompromised hosts may go unnoticed or resemble an upper respiratory infection. The foci of infection become walled off and both may calcify (Ghon or Ranke complex). However, the infection remains dormant for many years as a possible source of future infection—termed reactivation or post-primary tuberculosis. In some patients, and more frequently in immune-compromised hosts, the initial pathogenic infection cannot be immunologically contained, and the patient develops a systemic infection either due to hematogenous dissemination as miliary tuberculosis or as progressive pulmonary parenchymal disease termed progressive primary infection (344–346).

Primary tuberculosis may affect any lobe but has a slight predilection for the lower lobes whereas reactivation tuberculosis most typically occurs in the posterior and apical regions of the upper lobes (347). However, it must be noted that atypical sites for reactivation are frequent in patients who are immunocompromised, particularly with HIV (348–350). Both primary and reactivation infections may present as areas of parenchymal consolidation; however, reactivation tuberculosis is associated with a significantly higher incidence of associated cavitation (Fig. 44). When cavities in reactivation tuberculosis erode into the bronchial tree, endobronchial dissemination may occur resulting in the typical tree-in-bud appearance, as described further in the section pertaining to micronodular disease (347,351,352).

Nodular foci of tuberculous disease may result from either primary or reactivation tuberculosis and resemble either a solitary lung neoplasm or metastatic disease. With time, a proportion of such lesions, termed tuberculomas, may develop central or diffuse calcification indicative of their etiology. Adenopathy, often low-density, and pleural effusions occur in both forms of the disease; however, more complex empyema and bronchopleural fistulas are more common in reactivation tuberculosis, particularly in the chronic phase (353–356). During this chronic phase of infection irregular nodular densities may develop in the lung apices, usually associated with cavity formation, reticular scarring, and consequent traction bronchiectasis (357).

Nontuberculous mycobacterial infection. Atypical mycobacterial infections are caused by a large number of mycobacterial species that are ubiquitous in the soil and water and are of low virulence. Person to person spread is believed not to occur. Infection primarily affects the lung and skin. The most common causes of atypical mycobacterial lung infection are the *M. avium* and *M. intracellulare* species, commonly referred to as a single entity

termed *M. avium* complex (MAC). Other pathogens in the atypical mycobacteria category include *M. kansasii*, *M. xenopi*, *M. chelonae*, *M. fortuitum*, *M. goodii*, and *M. abscessus*. These diseases produce comparable disease patterns although the severity and extent of infection may vary, as do the treatment regimens (358). Coinfection with more than one species is frequent, and the detection of these organisms often depends on the extent to which microbiological differentiation is pursued (359).

Pulmonary infection occurs via inhalation of organisms. Unlike tuberculosis, primary and reactivation phases are not considered to occur, rather the manifestations of disease depend on the patient's age, immunity, the presence of preexisting lung disease such as bronchiectasis, and other unknown factors (47,360–362).

The classical description of pulmonary MAC infection pertains to elderly male patients with advanced chronic obstructive pulmonary disease (COPD) in whom infection produces a distribution and CT appearance of apical disease that is radiographically indistinguishable from reactivation tuberculosis. The disease is chronic and slowly progressive over a period of months or years (363,364). Disseminated MAC infection was subsequently described in patients with acquired immunodeficiency syndrome and presents typically as diffuse lymphadenopathy in the thorax and abdomen reflecting the widespread nature of infection (347,365). Increasingly, MAC infection is appreciated in elderly women also (358). The pattern of disease is strikingly different in women. Bronchial wall thickening and bronchiectasis is common, most typically in the inferior middle lobe and lingula, although when extensive all lobes are affected in a patchy distribution (Fig. 25) (364,366,367). The lungs are frequently hyperinflated in these patients due to air trapping from airways disease (368). COPD or even a smoking history is not infrequently absent. In these patients, foci of tree-in-bud opacity and centrilobular nodules on CT are indicative of a bronchiolitis (369). Small focal areas of parenchymal consolidation may occur, although lobar or extensive consolidation is uncommon. In addition, larger nodules of granulomatous inflammation may be present. Infrequently, cavitation of a minority of these nodules is appreciated (370). These larger nodules may also occasionally appear in the absence of other airway manifestations, and in these cases differentiation from neoplastic nodules is challenging. In general, although the course of this pattern of disease is slowly progressive, there is a quite variable evolution. The disease may pass through phases of quiescence and exacerbation independent of treatment, typically resulting in areas of “waxing and waning” disease at CT.

Fungal diseases

Nearly all fungal infections may result in parenchymal nodules, many of which may cavitate. The majority of

these diseases are uncommon with the exception of regional geographic exposure to histoplasmosis in the southeastern United States or coccidioidomycosis in the southwestern United States, Central, and South America. Of the non-geographically dependent or non-endemic diseases, infections with *Aspergillus* in neutropenic hosts and with cryptococcosis in immune-compromised hosts including transplant recipients are also relatively common (371,372).

Fungal infections may present with a variety of parenchymal appearances that will vary according to a patient's immune status and include miliary infection, larger nodules, cavitory nodules, and parenchymal airspace disease. Radiographically, therefore, these may be difficult to distinguish and, therefore, emphasis is placed on these commoner conditions and their differentiating features.

Histoplasmosis. Histoplasmosis is caused by inhalation of the fungus *Histoplasma capsulatum*, a soil-based organism found in the river valleys of the southeastern United States, particularly prevalent in soil contaminated by bird or bat excrement. The organism causes a wide variety of predominantly nodular pulmonary infection manifestations (373).

Initial inhalation and infection results in single or multifocal areas of parenchymal consolidative infection, with migration of the fungal organisms to the hilar and mediastinal nodes and hematologically to other organs, in particular, the spleen. This phase of the infection is usually self-limited, resolving without residua or small focal calcified nodules. In children or the immune compromised, this initial resolution of infection may not occur, resulting in a disseminated systemic infection with progressive chronic cavitory pulmonary disease that mimics tuberculosis. CT appearances of disseminated disease may include macronodular, military, or multifocal consolidative findings. There may be accompanying adenopathy that in time may become calcified (374).

Occasionally, acute epidemics of histoplasmosis may occur following release of large amount of organisms, often from a single source such as when demolition or construction disrupts an area with a large number of organisms. In these cases, infection with a large inoculum results in a pattern characterized by multiple nodules measuring up to 5 mm in size that appear in the lung parenchyma during the acute phase.

Larger single or multiple focal nodular lesions called histoplasmosis measure up to 4 cm in size. These lesions are akin to tuberculomas and may develop calcification centrally or in a laminated fashion during healing over a period of only a few months. These lesions may be surrounded by smaller satellite calcified nodules.

Rarely, a chronic form of pulmonary histoplasmosis infection develops, usually forming in areas of lung destroyed by emphysema. The appearances mimic reactivation

tuberculosis with fibronodular disease in the lung apices, although cavitory appearances are less common. In trying to differentiate tuberculosis from histoplasmosis, the presence of multiple splenic calcifications is a feature that is more commonly associated with histoplasmosis (375). In chronic histoplasmosis infections, calcific fibrosing mediastinitis is a feature occasionally present and seen with or without fibrocavitory disease (376,377).

Coccidioidomycosis. Primary coccidioidomycosis infection results from inhalation of airborne spores of *Coccidioides immitis* that reside in the arid conditions of desert soils. Infection is asymptomatic in the majority of patients and in the remainder results in only a short-term flu-like illness. In a small minority of cases, the primary phase of infection remains symptomatic after six to eight weeks and is termed persistent coccidioidomycosis. This is more likely to occur in the immune compromised, diabetics, and the elderly (378). In these cases, hemoptysis is common and patients are often markedly systemically ill. Typical CT appearances include foci of consolidation or coccidioidal nodules. Coccidioidal nodules are areas of rounded pneumonia, usually measuring less than 2 cm. These lesions may grow rapidly to sizes as large as 6 cm and frequently forming thin-walled cavities. Calcification is, however, unusual. Nodal enlargement occurs in approximately 20% of cases, may be marked, and may occur occasionally in the absence of visible parenchymal disease (379).

Chronic coccidioidomycosis infection is a relatively uncommon manifestation and mimics reactivation tuberculosis with an upper lobe process. Miliary infection is rare, with a high mortality, and may occur during persistent initial infection, chronic fibronodular disease, or systemic dissemination of disease. Systemic dissemination is a rare complication, nearly always fatal, occurring in less than 1% of cases, invariably immune-compromised hosts (378).

Aspergillosis. *Aspergillus* infection occurs with a variety of *Aspergillus* species, most frequently *Aspergillus fumigatus*, a dimorphic fungus found in decaying and molding vegetation. The appearance of disease depends on the host immunity and the underlying pulmonary architecture (380).

Aspergilloma, or mycetoma, is an accumulation of fungal hyphae that develops in an area of destroyed lung parenchyma in an immune-competent host, often a pre-existing apical cavity formed from chronic mycobacterial infection or a saccular area of bronchiectasis. Initially, focal pleural thickening may be the only manifestation of *Aspergillus* infection. With time an accumulation of hyphae results in the CT appearance of a sponge-like ball of hyphae within the prior cavity. This may result in the typical "air-crescent sign," a small lucency separating the dependent fungus ball from the anti-dependent wall of the cavity (Fig. 45) (381,382). The air-crescent sign that

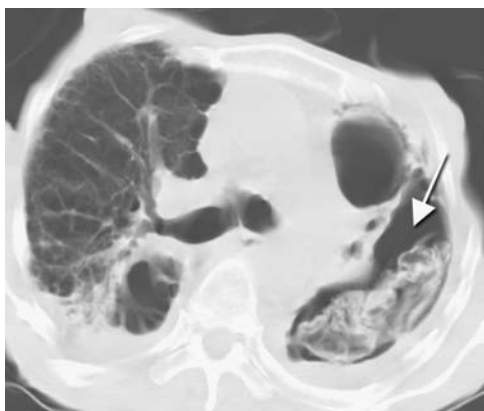


Figure 45 Tuberculosis with secondary aspergilloma infection. There is evidence of fibrosis and postinflammatory bronchiectasis in the posterior right upper lobe. In the posterior left upper lobe a serpigenous collection of aerated material lies dependent within a large preexisting tuberculous cavity. There is a rather thick air-crescent superior to this aspergilloma in this case (arrow).

was described initially with the angioinvasive form of aspergillosis, however, has been utilized to describe similar appearing findings in different forms of *Aspergillus* infection. The appearance may be confirmed by patient decubitus or prone repositioning, confirming the mobility of the fungal ball.

Semi-invasive aspergillosis occurs in immune-competent or marginally immune-compromised individuals such as diabetics, alcoholics, or chronic malignancy. Typical manifestations include an area of focal consolidation in the apices of the lung, with or without preexisting cavitory disease. The consolidation progresses over months to become a cavitory lesion. Progressively, an air crescent may form and the lesion transforms into a progressively thinner-walled cavity with a contained fungus ball, similar in appearance to a mycetoma (383,384).

Angioinvasive aspergillosis is a hemorrhagic, necrotizing pneumonia that occurs in immune-compromised hosts, particularly those who are neutropenic following bone marrow transplantation or chemotherapy (371,385,386). In these patients multiple nodular areas of ill-defined parenchymal opacity develop, consistent with foci of rounded pneumonia. These lesions may often appear solid centrally, with a peripheral “halo” representing hemorrhage surrounding the lesions. Over a period of days, usually during the recovery phase, approximately 50% of cases will demonstrate development of a peripheral air crescent caused by hyphal vascular invasion, resulting in central lung infarction and the formation of retracted central lung sequestrum separated by air from the viable nodule periphery (Fig. 45) (98,380,387–389). Angioinvasive aspergillosis is frequently associated with airway-invasive aspergillosis in which case hyphal invasion of

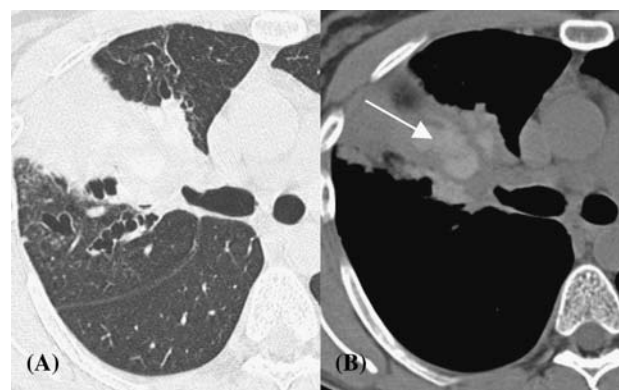


Figure 46 Allergic bronchopulmonary aspergillosis (ABPA). One-millimeter HRCT sections (A) lung windows, (B) medial-sternal windows. Note the large aerated varicoid and cylindrical bronchiectatic airways in the right upper lobe. Also note the relatively pathognomonic high density secretions in the mucoid impacted airways (arrow), which reflect the retention of manganese and magnesium because of altered clearance metabolism in these airways. Abbreviation: HRCT, high-resolution technique.

the airways results in a bronchiolar spread of infection (390).

Allergic bronchopulmonary aspergillosis is the final variant of *Aspergillus* infection that occurs in asthmatics and is mediated by a hyperreactivity to *Aspergillus* that has colonized the airways. This disease process is associated with eosinophilia and results in marked central bronchiectasis and mucoid impaction rather than a nodular pattern (Fig. 46) (391–393).

Cryptococcosis. Cryptococcosis is caused by inhalation of *Cryptococcus neoformans*, a yeast-like encapsulated fungus that resides in soil, often contaminated by bird excrement. The majority of symptomatic patients affected by the disease are immune compromised, either from HIV, diabetes, lymphoproliferative disorders, or drug-induced immunosuppression related to solid-organ transplantation.

The patterns of infection with cryptococcal disease are variable, but a frequent presentation is the presence of a solitary parenchymal nodule or mass. These lesions may be large measuring 10 cm or more. Cavitation, lymphadenopathy, and pleural effusions are uncommon in immune-compromised hosts but occur more frequently in immunocompetent individuals (394,395). When single or multiple, the lesions may be difficult to differentiate from neoplastic lung diseases (Fig. 47) (396,397). Frequently, biopsy is required to exclude malignant etiologies when suspicion for neoplasia exists, even in the presence of *C. neoformans* in sputum or bronchial washings, as the presence of these organisms may reflect nonpathogenic airway colonization in COPD.

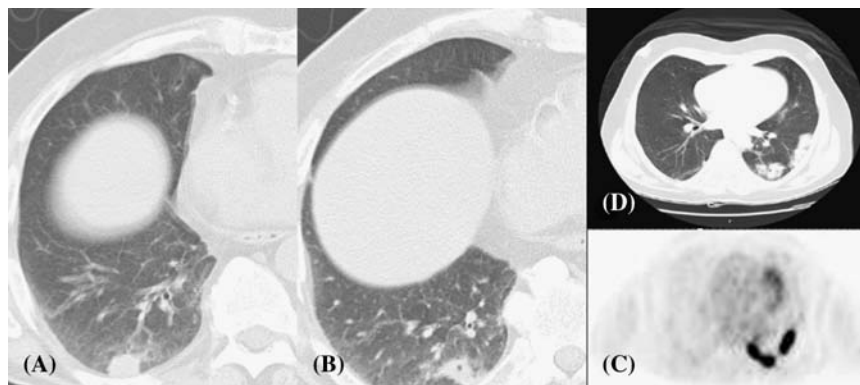


Figure 47 (A) and (B) Cryptococcal infection: 5-mm CT images show two basilar nodules are present in a diabetic debilitated patient. Although one of the lesions is cavitory, there are no specific features to distinguish these lesions from neoplastic nodules or other bacterial or fungal infections. Diagnosis in this case was made at transbronchial biopsy and confirmed by regression on treatment. In another patient receiving chemotherapy for lymphoma, a PET/CT (C) and (D) shows intense metabolic activity corresponding to the left lower lobe nodules, some of which are confluent on CT. This was also a cryptococcal infection.

A large single lesion or multifocal areas of mass-like consolidation are recognized patterns of infection by cryptococcosis. Few if any air-bronchograms may be present, and cavitation and adenopathy are relatively unusual. Resolution tends to occur without the volume loss and fibrocavitary changes seen in tuberculosis and other granulomatous disorders (289,394).

Miliary dissemination of infection is the least common appearance of pulmonary cryptococcosis and is indistinguishable from other etiologies of miliary infection. Such systemic dissemination occurs most commonly in immune-compromised hosts and has a predilection for involving the meninges, resulting in cryptococcal meningoencephalitis (398,399).

Septic emboli. Septic emboli may be caused by a variety of organisms and arise from microscopic thrombi that contain organisms and embolize to the pulmonary arterial system of the lungs. Typically, indwelling catheters, right heart valvular endocarditis and vegetations, or infected peripheral thrombophlebitis are sources of septic emboli. The incidence is greater in immune-compromised hosts, particularly intravenous drug abusers as these patients are additionally predisposed to right heart endocarditis and thrombophlebitis.

The hallmark of septic emboli is the presence of multiple pulmonary nodular densities, many of which are subpleural or basilar in distribution given their hematogenous distribution. The nodules may be rounded or triangular in shape with their apices directed toward the pulmonary hilum, resembling sterile infarcts. As the process is related to small vessel embolization by infective material, the larger vessels appear normal (400). However, frequently small vessels are prominent and directed into the apex of triangular opacities, termed the so-called “feeding vessel” sign. Up to half of the lesions may be

cavitory. Characteristically lesions frequently appear in different phases of evolution, suggesting continuous embolization to the lung. Effusions are commonly present. Notably, although the diagnosis is confirmed by blood cultures, the CT appearances may precede the development of positive cultures and, therefore, particularly impact patient management (401).

Noninfectious Inflammatory Etiologies

Vasculitides

Wegener’s granulomatosis classically describes a triad of a granulomatous necrotizing angiitis involving the upper respiratory tract, the lungs, and the renal parenchyma. Usually clinical presentation occurs with upper respiratory tract pain or less frequently pulmonary involvement resulting in hemoptysis. Renal involvement is usually discovered during clinical investigations that also reveal a high erythrocyte sedimentation rate and a positive antineutrophil cytoplasmic antibody (402). More recently, a limited form of Wegener’s granulomatosis has been described involving only the lung parenchyma (402,403).

The CT appearances of classical or limited Wegener’s are identical and are similar to those of septic emboli (Fig. 48). Multiple pulmonary nodules may be as large as 10 cm and demonstrate irregular and thick-walled cavitation. The angiocentric nature of the disease is revealed by the presence of feeding vessels at the apex of many of the nodules. In certain patients, areas of parenchymal airspace disease may also be present and likely relate to pulmonary hemorrhage, which has been shown to be a poor prognostic indicator. Effusions and adenopathy are unusual (402,404–406).

Other granulomatous vasculitides may present with solid or cavitory nodules; however, in these conditions nodular manifestations are atypical, and there may be other



Figure 48 Wegener's granulomatosis: 5-mm CT section. There is a cavitary nodular density in the periphery of the left upper lobe and a solid nodular lesion in the subpleural right lower lobe. These appearances are not specific and may be caused by a variety of etiologies including metastatic disease. However, the appearances of peripheral lesions in various stages of cavitation should, also raise the possibility of septic emboli, which may be indistinguishable from Wegener's granulomatosis.

ancillary radiological findings that distinguish the disease from Wegener's disease. For example, allergic angiitis and granulomatosis (Churg-Strauss syndrome) more typically results in fleeting parenchymal airspace disease seen in the context of an asthmatic with eosinophilia. In these patients, nodular disease, when it occurs, is usually noncavitary (407). Bronchocentric granulomatosis affects asthmatics that are usually concomitantly affected by allergic bronchopulmonary aspergillosis and mucoid impaction. In these patients the pulmonary vasculitis is not the primary etiological mechanism, but rather is secondary to extension of necrotizing granulomatous involvement of the bronchial wall (408). Necrotizing sarcoid granulomatosis is a focal version of sarcoidosis that results in several larger nodules that tend to coalesce. Lymphomatoid granulomatosis may mimic Wegener's disease with multiple cavitary lesions; however, this condition is now more correctly categorized as a frank B-cell lymphoma.

Rheumatoid nodules

Rheumatoid necrobiotic nodules are exceedingly rare manifestations of rheumatoid arthritis. They appear as relatively well-defined peripheral nodules that range in size from subcentimeter to several centimeters (Fig. 49). Solitary lesions occur in approximately one-quarter of cases, and cavitation occurs in approximately half of the cases resulting in smooth walled lesions. The nodular densities may grow slowly and have been rarely reported to erode into the ribs or the pleura resulting in bronchopleural fistula or hydropneumothorax formation. Under-

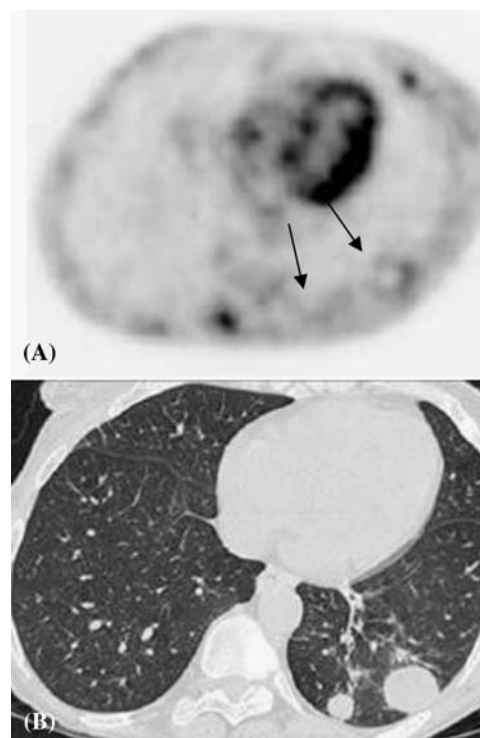


Figure 49 Patient with rheumatoid arthritis. (A) Correlated axial PET image demonstrates rim of mild FDG uptake in both nodules (arrows) (with central photopenic metabolically inactive area, most likely related to central necrosis or cavitation). (B) Axial view of CT chest demonstrates two pulmonary nodules in left lower lobe. Fine needle aspiration cytology of the larger lesion was obtained, which revealed necrotizing granulomatous inflammation with no features of malignancy. Osseous uptake relates to fractures.

standably, the lesion, therefore, may mimic a primary lung neoplasm. Diagnosis of rheumatoid nodules depends upon knowledge of the history of rheumatoid disease, which is almost always seropositive (90%). Biopsy of lung parenchymal lesions is often required for confirmation. Histopathology demonstrates a characteristic appearance identical to that of a subcutaneous rheumatoid nodule with a fibrinoid necrotic center surrounded by palisading histiocytes, peripheral plasma cells, and lymphocytes. Subcutaneous nodules are almost always also present in these patients, although the pulmonary nodules may predate the development of subcutaneous nodules rarely.

On FDG PET scan, rheumatoid nodules may demonstrate variable activity, from very mild FDG uptake, suggesting benign disease (Fig. 49) (409), to intense FDG-avidity, giving a false-positive result for malignancy (410). Further studies are needed to define the role of FDG PET in the evaluation of rheumatoid arthritis nodules.

Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown etiology that is characterized by the presence of noncaseating granulomas in the organs of involvement. However, there are many disease processes that may result in these histological appearances, and in the absence of definitive diagnostic serological tests, the diagnosis of sarcoidosis is often supported by typical radiological findings. In a patient with suspected sarcoidosis, the purpose of CT imaging is not only to identify pathognomonic or supportive features but also to exclude other granulomatous diseases, in particular tuberculosis, as caseating granulomas may occasionally be missed due to sampling error at transbronchial biopsy. Established entities have been described that mimic sarcoidosis and include inhaled foreign-body granulomatoses and a few sarcoid-like disease states have been more recently described. These include firefighters with airborne particulate exposure and patients treated for hepatitis C with interferon- α who have an immunologically mediated sarcoid-like reaction (411–413). A known association between sarcoidosis and lymphoma exists, called “sarcoidosis-lymphoma syndrome” (414).

Sarcoid has a range of pulmonary CT appearances, many of which appear nodular. Parenchymal involvement in the early potentially reversible phase of disease is frequently accompanied by symmetrical mediastinal and hilar adenopathy, whereas effusions are rare. Parenchymal involvement typically involves the upper and mid-lung regions in a peribronchovascular micronodular pattern (see Fig. 50 and micronodular disease below). However, larger nodules measuring up to 1 cm that may be perilymphatic (Figs. 50 and 51) or randomly distributed are



Figure 50 One-millimeter HRCT image. Symmetric perilymphatic distribution of nodules in sarcoidosis. Note the thickening of the central perihilar peribronchovascular structures, also known as the axial interstitium. Multiple nodular densities are noted in the perifissural regions. These features are highly characteristic of sarcoidosis. *Abbreviation:* HRCT, high-resolution technique.

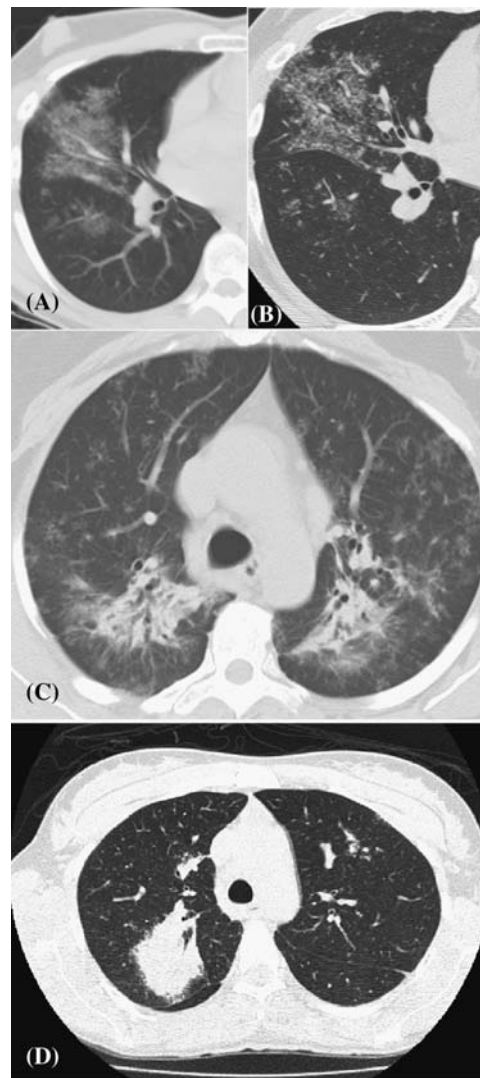


Figure 51 Sarcoidosis. “Alveolar sarcoidosis” on (A). 7-mm and (B) 1-mm HRCT images. The thicker section (A) suggests the presence of ground-glass or even parenchymal consolidative opacity. However, the thin corresponding HRCT section (B) properly characterizes that this appearance of “alveolar sarcoidosis” is genuinely due to a conglomeration of multiple tiny perilymphatic nodules. In fact genuine ground-glass opacity is exceedingly rare in sarcoidosis. (C) Five-millimeter axial CT image. Confluent granulomatous fibrotic masses. In this advanced case of sarcoidosis the parenchymal perilymphatic disease has progressively developed into a fibrotic mass. The lesions are frequently in the posterior upper lobes or superior segment of the lower lobes and are associated with fibrosis in the remainder of the parenchyma. Note the tractional bronchiectasis within the “masses.” (D) In alveolar sarcoid, the conglomeration of nodules may also lead to consolidative areas or nodules without tractional or fibrotic changes or evidence of diffuse peribronchovascular nodules. Note the multiple small nodules in the periphery of the consolidative mass, which has one air bronchogram within. *Abbreviation:* HRCT, high-resolution technique.

also recognized as a less common presentation of sarcoidosis. These larger nodules may contain air-bronchograms and coalesce, although cavitation is rare (415–418). On occasion, nodular “airspace” consolidation or “ground glass” opacities develop in a pattern termed alveolar sarcoid. In actuality this appearance is not truly due to alveolar disease but results from an interstitial carpeting by a myriad of micronodules that coalesce and simulate the appearance of airspace (Fig. 51) (419,420).

As the disease in sarcoidosis progresses, it may become less nodular and more reticular in nature as a fibrotic phase develops. This fibrosis, once again, involves the upper and mid-regions of the lungs and typically may also spare the anterior- and posterior-most lung parenchyma. Sarcoid fibrosis causes retractile tractional bronchiectasis of the central airways that are pulled toward the lateral pleural surface (421). During this phase of fibrosis, adenopathy may completely resolve. In certain cases fibrosis becomes progressively confluent and “mass-like” resulting in a progressive-massive fibrosis-like appearance in the upper lobes. The appearance of this resembles the process in patients with silicosis and coal workers’ pneumoconiosis (Fig. 51). Secondary cavitation within the regions of progressive massive fibrosis may occur in sarcoidosis (422).

Assessment of disease activity is critical for determining whether therapy is necessary. CT may clarify the level of activity of the inflammatory process with high specificity (421,423–426). Gallium-67 imaging has been widely used in the diagnosis of sarcoidosis: a characteristic pattern of uptake within the chest has been described as the “lambda sign”: paratracheal and bilateral hilar uptake typical of sarcoidosis. Another pattern of uptake is called the “panda sign,” caused by uptake within the lacrimal and parotid glands (427). When present together, the panda sign and the lambda sign are highly specific for sarcoidosis (428).

Multiple reports have shown increased FDG uptake in sarcoidosis (Fig. 52) (429–432). However, FDG uptake in sarcoidosis is nonspecific and is not generally useful in making an initial diagnosis. Moreover, intense FDG uptake within lymph nodes and parenchymal organs can be challenging when differentiating between sarcoidosis and lymphoma or diffuse metastatic disease. Nevertheless, the patterns of FDG uptake in some cases may be suggestive of sarcoidosis, reducing the number of false-positive results in patients being evaluated for cancer. The most common pattern appears similar to that of ^{67}Ga images, i.e., intrathoracic lymphadenopathy, with bilateral hilar uptake extending into the mediastinum and lung parenchyma. This can be seen in up to 85% of patients (433). The second pattern in patients with sarcoidosis consists of multiple foci of intense uptake in lymphadenopathy (cervical and/or abdominal lymphadenopathy in 30% of cases), which can

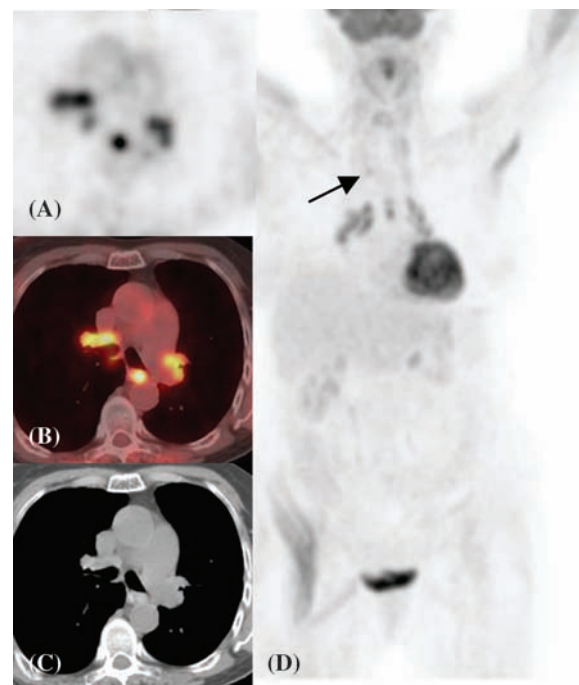


Figure 52 Sarcoidosis on PET/CT. (A–C) Axial views of PET/CT scan showing intense FDG uptake in bilateral hilar lymphadenopathy in a patient with active sarcoidosis. (D) Maximal intensity projection view of a patient with sarcoidosis. The bilateral hilar FDG uptake shows a characteristic “delta sign” pattern which has been described in Gallium scans as typical for mediastinal involvement from sarcoidosis. In addition, a right paratracheal node is involved (arrow). Abbreviation: MIP, maximal intensity projection.

be extensive in size in 10% of patients (434). Active uptake in the spleen with splenomegaly is common with this pattern, sometimes associated with active low-density focal lesions within the spleen (435). FDG PET at this time does not have an acknowledged role in the initial diagnosis of sarcoidosis; however, FDG PET may prove to be useful in the management of patients with known sarcoidosis. FDG PET findings have been shown to correlate well with disease activity (8). Additionally, it has been suggested that patients with an abnormal chest radioiograph, a high angiotensin-converting enzyme level, and a normal PET scan may remain well without treatment (436).

Amyloidosis

Amyloidosis is a disorder in which abnormal accumulation of amyloid, a protein predominantly consistent of autologous protein fibrils, is deposited extracellularly throughout the body. In the past, amyloidosis was categorized as idiopathic primary or secondary amyloidosis, the latter usually the sequela of chronic inflammation or suppuration. Currently, at least 25 variants of amyloid protein have been identified so that a reclassification of amyloidosis

according to protein morphology has become necessary. Nonetheless, the radiological features of amyloid are similar for many of these protein subtypes, and the effects of amyloid deposition can be analyzed according to whether the distribution is systemic, involving multiple organs, or localized to limited organ systems (437).

In systemic amyloidosis pulmonary involvement is frequently present but seldom of clinical significance. The distribution of disease is typically along the septa and pleural surfaces and may be nodular and perivascular in nature, similar to lymphangitic disease (438,439). Pulmonary arterial hypertension may develop when perivascular involvement is present. However, it must be noted that in systemic amyloidosis cardiac involvement is not infrequent and may result in smooth interlobular septal thickening that may mimic amyloid involvement. Similarly effusions are not uncommon in systemic amyloidosis and may be due to cardiac involvement or pleural amyloid (440,441).

Localized amyloidosis can involve any organ or body region in isolation. In the thorax the parenchyma and the airways are about equally commonly affected and occasionally are simultaneously involved. Parenchymal nodular involvement in amyloidosis is typically the result of localized disease. Nodules are nonspecific in appearance, typically well defined but may also appear irregular or spiculated (Fig. 53). Although cavitation is rare, calcifi-

cation is common, reported as occurring in up to 50% of cases (442–444).

Localized amyloidosis in the airways is more frequently diffuse through the central airways rather than focal. The disease is chronic and progressive and may recur despite bronchoscopic resection or laser therapy. Most typically patients are symptomatic, often presenting with symptoms of central airways restriction resembling asthma or present with symptoms of peripheral obstructive infections (445–449). Localized amyloidosis may also present as a smooth alveolar septal infiltration or as a micronodular form of the disease resembling the pulmonary appearances of systemic amyloidosis (438,439). Unlike morphologically comparable parenchymal involvement in systemic amyloidosis, patients are usually symptomatic, and the prognosis is poor. In this entity progressive interstitial confluent disease may occur including coalescence of micronodules into larger opacities, parenchymal calcification and cyst formation.

Vascular Etiologies That Present as Masses or Nodules

Pulmonary infarcts

Pulmonary infarcts may appear as focal nodules in the subpleural lung parenchyma. Infarcts are frequently triangular in shape with their apices directed toward the lung

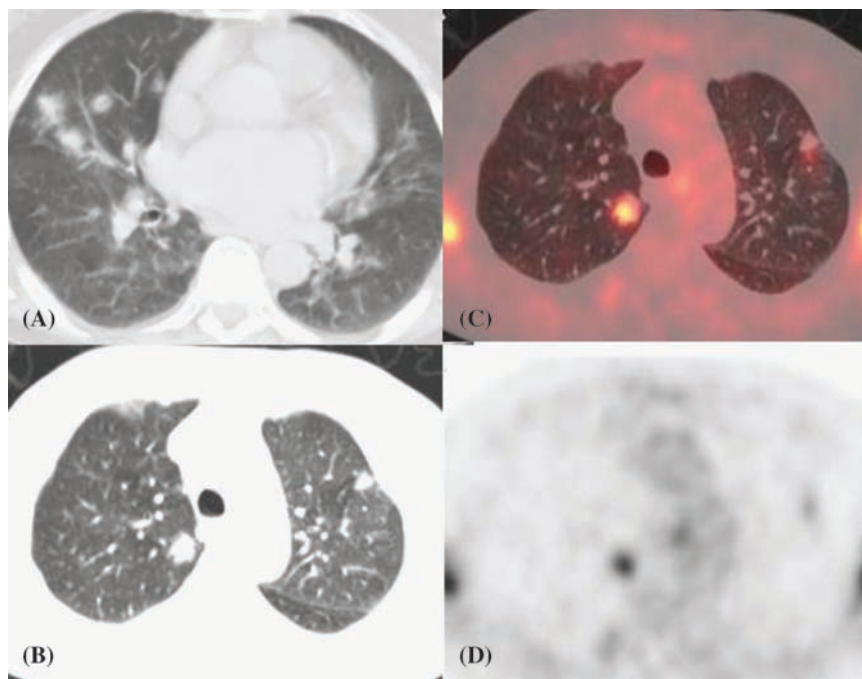


Figure 53 Nodular amyloidosis. (A) Five-millimeter CT image from a PET/CT study. CT demonstrates multiple nonspecific nodules in a patient with localized amyloid and pulmonary nodular manifestations. There are no distinguishing features in this phase of amyloidosis. The patient had a known remote malignant history and underwent biopsy to exclude metastatic disease. The diagnosis was confirmed by birefringent polarized light microscopy. (B) CT slice at a lower level with (C) fused and (D) corresponding PET images show metabolic activity fusing to the amyloid nodules.

apex. Not infrequently they may, however, also appear as more rounded or irregular opacities. Air-bronchograms or mottled lucency within these lesions is frequently seen in the acute phase. Although these findings do not pose a diagnostic dilemma on a contrast-enhanced CT study, particularly if the study is performed with a pulmonary embolism protocol, the detection is more challenging on noncontrast or nondedicated studies. Opacities that reflect pulmonary hemorrhage or reperfusion edema may resolve very rapidly, while genuine infarcts resolve more slowly over a period of four to six weeks to a central scar. Unlike rounded pneumonia, which resolves in a patchy fashion, infarcts resolve from the periphery inwards, described as a “melting ice-cube.” Cavitation may occasionally occur in sterile infarcts, although its appearance is more typical of septic emboli or secondary infection of an originally sterile infarct. Sterile cavitation is more common in larger lesions greater than 4 cm and typically occurs in the subacute phase (>2 weeks).

FDG PET uptake has not been extensively reported in relation to pulmonary embolism (450) and to pulmonary infarcts, in which uptake can be variable (59,451). Activity may be possibly due to inflammatory cells involved in the repair process in the infarcted lung and at the organizing thrombus. Uptake in microemboli has been reported occasionally after paravenous infiltration of the dose, presumably due to incorporation of tracer into microthrombi at the injection site. On PET/CT, there will be no CT correlate for the uptake (452).

Hematoma, contusions, and lacerations

Focal hematoma (or contusion) is the result of blunt trauma and may or may not be associated with other injuries such as rib fractures. Typically, the abnormalities appear patchy, peripheral, and nonsegmental in nature. As the fissures do not limit the transmission of force, the opacities have a nonanatomic distribution. Unlike focal infection, air-bronchograms are unusual because of blood within the airways. When extensive, the appearances of contusions may resemble airspace disease; when focal, they may resemble nodules or other parenchymal masses (453). Hematoma in the lung parenchyma typically appears within six hours of trauma, significantly resolving within 24 to 48 hours (454). Uptake on FDG PET in focal hematomas has not been reported, although uptake in associated rib fractures is commonly seen.

Parenchymal laceration is the result of a more forceful disruption of the lung parenchyma resulting when a shear injury causes a focal pulmonary tear. The laceration may initially be concealed within an area of contusion. Gradually the laceration becomes apparent as the contusion resolves, and the evolving pneumatocele become filled with hemorrhage, air or a combination of both presenting with an air crescent around a hematoma or an air-fluid level. Typically,

the laceration resolves over a period of weeks; however, occasionally lacerations may persist as a solid nodule that, in the absence of a history of trauma, could otherwise cause confusion, resembling a lung neoplasm (453). PET studies of parenchymal lacerations have not been reported.

Arteriovenous vascular malformations

Pulmonary AVMs are abnormal focal communications occurring between arteries and vein in the lung parenchyma. The lack of an intervening pulmonary capillary bed results in the absence of gaseous exchange. Therefore, AVMs act as right-to-left shunts. The majority of these lesions are congenital, more commonly occurring in the lower lobes and are multiple in approximately a third of patients. At least half of all AVMs are associated with systemic AVMs, in particular Osler Weber-Rendu syndrome. In these cases pulmonary AVMs are usually multiple.

The majority of AVMs are simple with a single feeding artery and single draining vein (Fig. 26). AVMs are considered complex if there is more than one feeding vessel, which occurs in approximately 20% of cases. The evaluation of more complex anatomy is enhanced by the use of intravenous contrast and reconstructions of narrow section thickness. In this regard, MDCT, particularly with 3D reconstruction, is equivalent to dedicated pulmonary angiography. In the absence of these technical factors, particularly if the CT component of a PET/CT examination is performed during quiet respiration, small feeding vessels may not be visualized, and AVMs may be misinterpreted as neoplastic abnormalities. Although no specific reports describing the appearance of pulmonary AVMs on FDG PET exist, it is expected that, like cerebral AVMs, these will not accumulate FDG (455).

Miscellaneous Nodular Conditions

Rounded atelectasis

Rounded atelectasis is a sequela of prior remote inflammation, occurring predominantly in patients who have associated pleural disease in the same location. Rounded atelectasis occurs most commonly in patients with asbestos-related pleural disease. The exact etiology of rounded atelectasis is unknown but postulated to result from an initial episode of atelectasis associated with a pleural effusion. The atelectasis fails to resolve as the effusion resorbs because the lung cannot fully re-expand due to residual fibrinous pleural adhesions. In these cases the lung becomes “infolded” (456–458). CT imaging may reveal a subpleural lesion that is partially irregularly marginated, often measuring several centimeters in size, and appearing morphologically similar to a primary bronchogenic malignancy. Three features are required for the confident diagnosis of an area of rounded atelectasis. These include focal pleural thickening adjacent to the

lesion, volume loss in the region of rounded atelectasis, and the “comet tail sign” indicating the whorled “infolded” vessels extending toward the pulmonary hilum (Figs. 54, 55) (459,460). Rounded atelectasis may demonstrate prominent enhancement despite its benign nature. Foci of rounded atelectasis usually remain stable, although may also gradually decrease or increase in size (461). Although reports suggest that round atelectasis is metabolically inactive, there may be mild uptake when chronic inflammation is still present (462). However, the activity is expected to be below the SUV threshold for malignancy.

Lipoid pneumonia

Exogenous lipoid pneumonia occurs as a result of aspiration of mineral oil laxatives or other hydrocarbons, most typically identified in the elderly. Gastroesophageal reflux and obstructive esophageal pathology are significant contributory factors in these patients. Although larger areas of

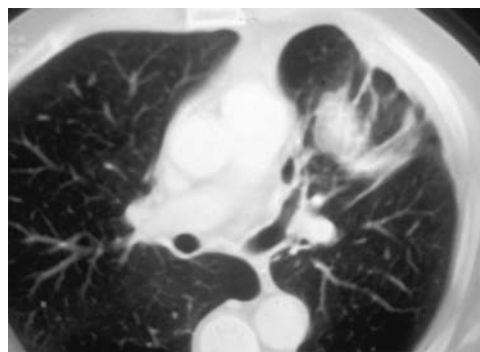


Figure 54 Rounded atelectasis in a patient with prior asbestos exposure—5-mm section. Superior aspect of a large mass-like density in the left upper lobe with irregular borders that form curvilinear bands that reach toward the hilum and the pleural surface in this case. Note also the anterior displacement of the lingular bronchus signifying volume loss in the left upper lobe and the pleural thickening along the left anterolateral pleural surface which are essential corroborative features for the diagnosis.

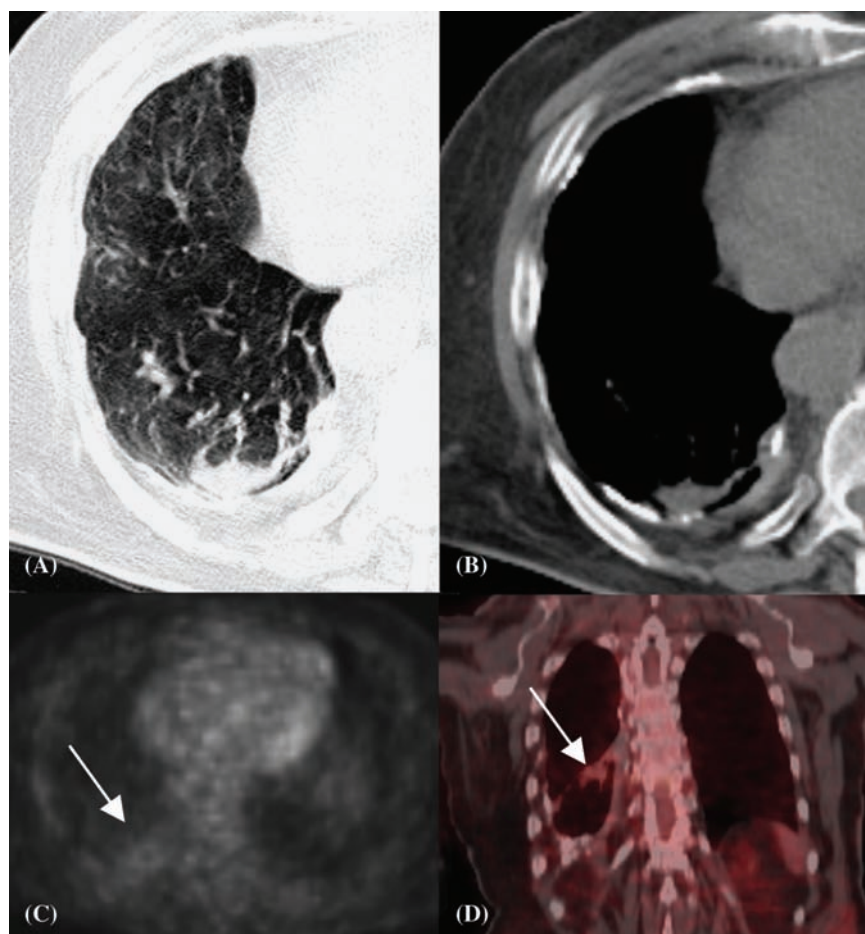


Figure 55 PET/CT of rounded atelectasis. The mass like density (A) in the right lower lobe is associated with volume loss and mild retraction of vessels toward the atelectatic mass. There is pleural calcification and thickening related to prior asbestos exposure (B). PET/CT was helpful for confirming the low metabolic activity (arrow) expected with rounded atelectasis, as shown on attenuation corrected axial (C) and coronal fused PET/CT (D).

parenchymal consolidation are more likely to be confused with parenchymal airspace infection, focal nodular and mass-like lesions may also occur, occasionally with spiculated margins. In these patients the demonstration of a low-density fat attenuation region with the lesion is essential for diagnostic confirmation (Fig. 23) (463–465). Cavitory change in these lesions does not occur *de novo* and is indicative of secondary infection usually by atypical mycobacteria. Lipoid pneumonia will appear quite active on FDG PET with (466) or without the presence of superinfection with mycobacterium (467).

Endogenous lipoid pneumonia occurs as either a result of accumulation of lipid-rich macrophages beyond a region of endobronchial obstruction (“golden pneumonia”) or as a result of toxicities from certain drugs that include amiodarone. In these patients, rather than a nodular appearance, parenchymal consolidation is the common feature with progressive interstitial interlobular septal thickening (465,468,469). False-positive FDG PET has been described in this entity as well (470).

Lymphocytic interstitial pneumonitis

Lymphocytic interstitial pneumonitis (LIP) is characterized by a diffuse lymphocytic infiltration of the interstitium of the lung parenchyma. LIP is associated with a variety of diseases including Sjogren’s disease and other autoimmune diseases, dysproteinemias, bone marrow transplantation, viral, and mycobacterial infections. In children, but not adults, HIV infection is a common association. Although sporadic cases of lymphomatous transformation have been reported in the literature, LIP is now considered a reactive lymphatic process rather than a genuine lymphoproliferative disorder (471). The commonest described features seen at CT include basilar predominant ground-glass opacity accompanied by reticular and nodular density. Larger subcentimeter nodules may also be identified. A hallmark of this disease is the progressive development of cystic lung disease, possibly secondary to a ball and valve effect occluding the small airways. The distribution of cysts is random affecting the entire lung parenchyma. The cysts are usually larger, measuring 2 to 5 cm, and less numerous than the cysts of the other idiopathic cystic lung diseases (lymphangiomyomatosis, tuberous sclerosis, Langerhan’s Cell Histiocytosis) (Fig. 56) (472). LIP on FDG PET has not been described.

Langerhan’s cell histiocytosis

Pulmonary Langerhan’s cell histiocytosis occurs in young patients, invariably with a smoking history. Early in the disease phase, the lung demonstrates multiple randomly distributed nodular densities, involving the entire parenchyma but frequently sparing the extreme inferior and anterior lung parenchyma. With time these nodules may

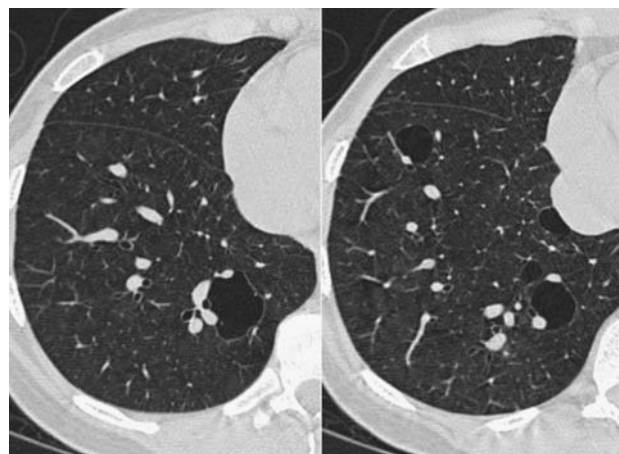


Figure 56 One-millimeter HRCT images. Cystic lung disease due to lymphocytic interstitial pneumonitis in a patient with Sjogren’s disease, a common association. The cysts are thin walled, sometimes demonstrating adjacent nodules. They may be absent or multiple, although 10–20 is the norm. *Abbreviation:* HRCT, high-resolution technique.

cavitate and progressively individual nodules may be difficult to identify as the lung becomes replaced by irregular and bizarre shaped cysts (Fig. 57). The cysts frequently are clustered in groups early on with subsequent involvement of the entire lung (473–475). This also, has not been described on FDG PET.

Diffuse Parenchymal Lung Disease

CT Diagnosis and Technique

Diffuse parenchymal lung disease patterns may be challenging to diagnose even with optimal CT technique. Diagnosis may require not only the evaluation of conventional thicker 3 to 7 mm collimation images but will frequently require supplementation with the use of images reconstructed using a HRCT technique. In this regard meticulous attention to the details of technique is required to obtain images of optimal image quality and, hence, diagnostic yield. There are several integral facets to HRCT technique. Most importantly, images must be reconstructed in a narrow section thickness of 1 to 1.5 mm using a high-frequency algorithm (frequently termed lung or bone algorithm) to minimize partial volume effects and increase spatial resolution. Spatial resolution is maximized by using a field of view for the reconstructions limited to the lungs alone. Finally, in general HRCT is a technique used to sample a diffuse process and therefore the images are reconstructed at intervals, generally of 10 mm. Although MDCT acquisition of volumetric data sets permits the reconstruction of contiguous HRCT data, the use of such data sets in practice is limited to occasional problem solving in occasional cases.

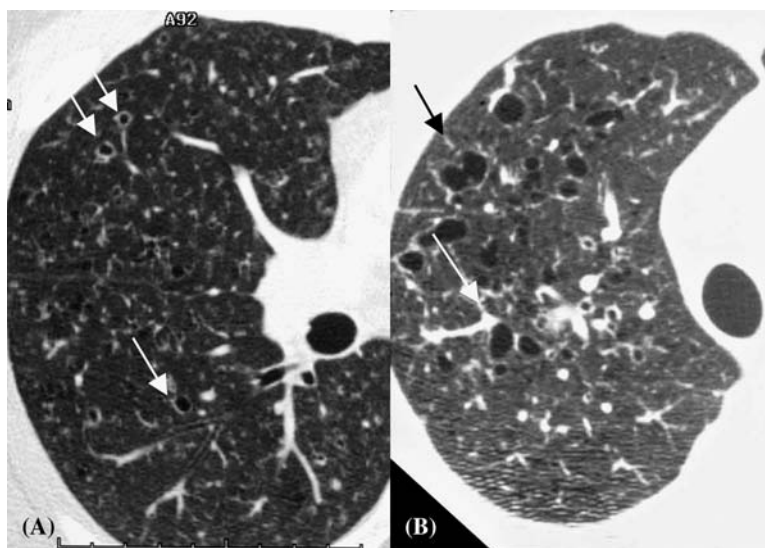


Figure 57 Langerhan's cell histiocytosis. (A) Early-phase example. Small solid nodules and other thicker-walled cysts are present (arrows). (B) Later-phase example: as the disease progresses the cysts become thinner walled and more bizarre shaped (arrows). They may become confluent with sparing of only the anterior most and inferior most lung parenchyma.

Contiguous HRCT data sets may generate as many as an additional 350 images, not only making interpretation a cumbersome task but adding significantly to data storage needs. Therefore, in select indications the use of non-contiguous coronal HRCT images is helpful such as when evaluating patterns of interstitial fibrosis and patients with small airways disease or bronchiectasis. Usage of optimal HRCT technique results in resolution of structures as small as 400 μ m, and is essential for evaluating structures within the secondary pulmonary lobule. In clinical practice as the CT component of a PET/CT acquisition is often obtained in quiet respiration, respiratory motion may preclude optimum HRCT technique and may, therefore, necessitate the performance of a separate dedicated thoracic CT acquisition including HRCT reconstructions at a later date.

The secondary pulmonary lobule represents the lung parenchyma subtended by each terminal bronchus and is the smallest unit of lung surrounded by its own septa. These interlobular septations are most developed at the lung bases and, therefore, the polygonal shape of these lobules measuring up to 1.5 to 2 cm is often best seen in these areas, particularly in the subpleural lung (Fig. 58).

The central portion of the secondary pulmonary lobule contains the terminal artery and accompanying bronchus. Unless pathologically thickened, the terminal bronchi are not usually visualized, and therefore the single central dot reflects the central artery of the lobule core structures. The lymphatic and venous drainage of the lung runs in the

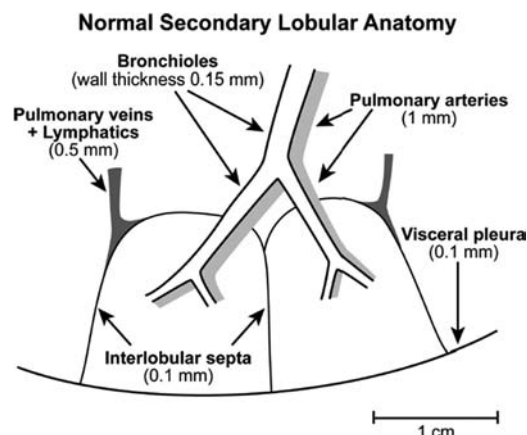


Figure 58 Anatomical representation of the normal secondary pulmonary lobule. *Source:* From Ref. 476.

periphery of the lobule contained within the interlobular septa. The lymphatics also run along the pleural and fissural surfaces and more centrally along the segmental, lobar, and main bronchovascular structures, the so-called "axial interstitium," to the pulmonary hila.

Frequently in diffuse lung disease, FDG accumulation will be seen depending on the disease activity. Initial categorization of diffuse lung disease may be based on CT

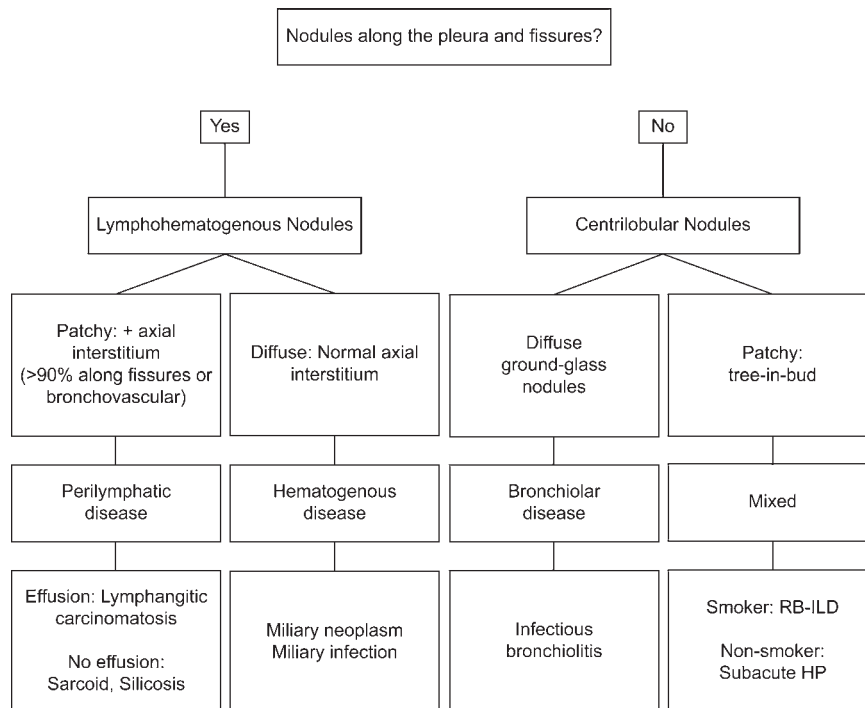


Figure 59 Algorithm for evaluation of diffuse micronodular lung disease.

categorization into distinct radiological patterns that are helpful for determining a limited differential or specific diagnosis. Radiological patterns may be differentiated into predominantly micronodular, reticular, increased density (airspace disease), or diseases with reduced parenchymal density.

Micronodular Pattern of Disease

Micronodular disease is characterized by the presence of multiple nodules smaller than 3 mm in size. The algorithm for evaluation of micronodular disease is summarized in the algorithm in Figure 59. Through a limited series of binary questions micronodular disease can be classified along different diagnostic pathways (476). The first issue for consideration is whether nodules contact the pleural or fissural surfaces. In cases in which this occurs the disease is lymphohematogenous; conversely if the nodules spare these regions the nodules are considered centrilobular in nature.

Lymphohematogenous nodules

Lymphohematogenous nodules are further characterized by determining whether the majority (80–90%) of nodules are distributed along the pleura, fissures, or bronchovascular structures. In cases in which this fact holds true, the disease is anatomically defined as a perilymphatic process (Fig. 60). The limited differential of perilymphatic dis-

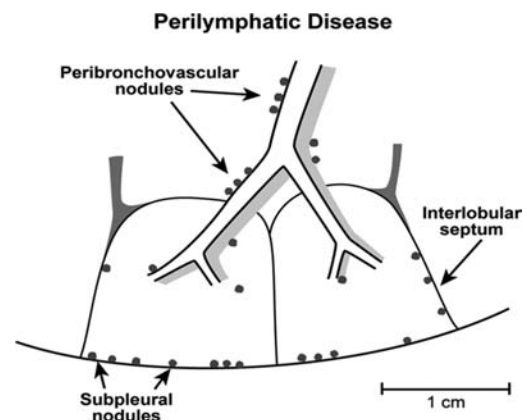


Figure 60 Distribution of perilymphatic nodules with regard to the secondary pulmonary lobule. The majority of nodules contact the fissures, interlobular septa, or axial interstitial core structures. The most common causes for this appearance are sarcoidosis or lymphangitic carcinomatosis. *Source:* From Ref. 2.

eases include sarcoidosis (and the radiographically similar but far less common silicosis) and lymphangitic carcinomatosis. The key differentiating features between sarcoidosis and lymphangitic disease are the absence of effusions in the former (Fig. 61) and the common presence of both effusions and nodular interlobular septal thickening in the latter (Fig. 61).

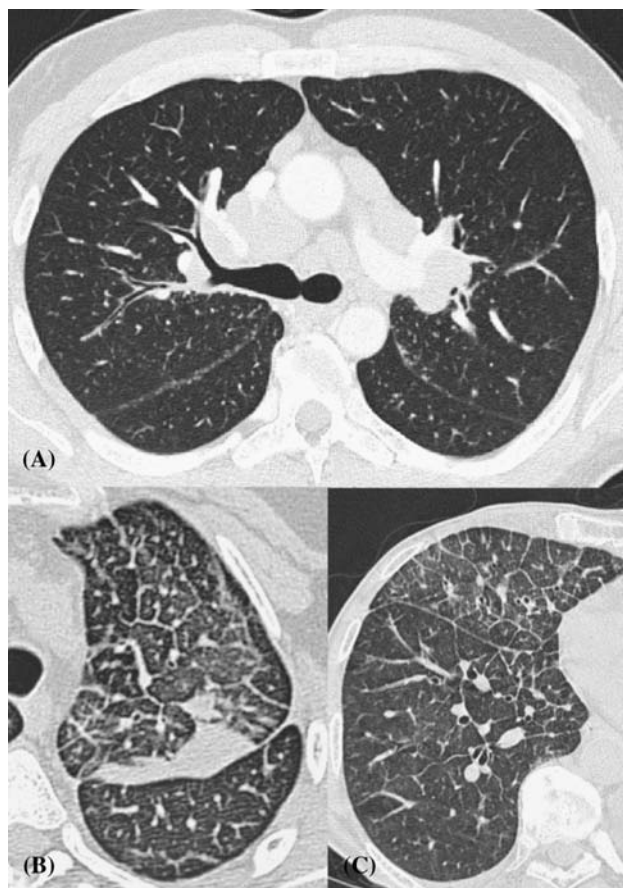


Figure 61 Lymphohematogenous nodules. Perilymphatic nodules (A) 1-mm HRCT image. There is symmetric perilymphatic distribution of nodules in sarcoidosis. Note the nodules along the central perihilar peribronchovascular structures, also known as the axial interstitium. Note the multiple small nodules along the fissures. Both the axial interstitium and subpleural regions contain many lymphatic structures, and therefore nodules in these areas are characteristic of perilymphatic disease such as sarcoidosis. (B) One-millimeter HRCT images show nodular interlobular septal thickening with a more mass like area adjacent to the left major fissure. These appearances are highly suggestive of lymphangitic carcinomatosis. (C) This shows smooth interlobular septal thickening in a different patient. In this second case the appearances proved to be due to benign lymphatic obstruction alone and resolved on treatment of a proximal central right hilar lesion (*not demonstrated*). *Abbreviation:* HRCT, high-resolution technique.

In cases in which only a minority of nodules is located in typical perilymphatic locations, the distribution is likely to be random (Fig. 62). The disease process is usually diffuse and may demonstrate a basilar predominance, and the distribution and pattern of disease are termed miliary. Miliary disease may be due to infection, most typically tuberculosis but also occasionally histoplasmosis, or miliary metastatic disease, typically thyroid, melanoma, or

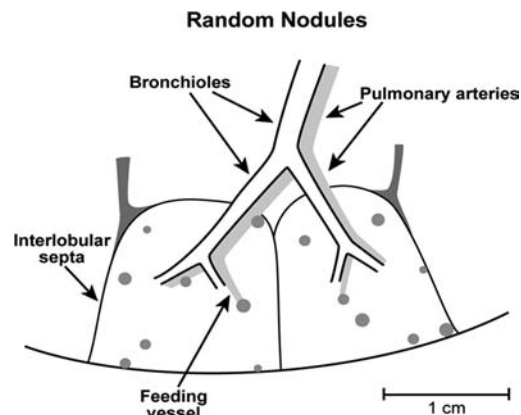


Figure 62 Distribution of random nodules with regard to the secondary pulmonary lobule. Note that although some nodules contact the fissures this is not the dominant pattern. The most common causes for this appearance would include miliary tuberculosis or miliary metastases. *Source:* From Ref. 2.

sarcoma primaries (Fig. 63) (344,477–479). Differentiation of miliary infection from miliary metastatic disease may be difficult and depends on the clinical scenario such as the presence of pyrexia or an immune-compromised state. The nodules in miliary metastatic disease may be slightly more variable in size, concurrent with the presence of larger metastatic nodules; however, this feature is not ubiquitous.

Centrilobular nodules

Patients with nodules that do not contact the pleura or fissures are centrilobular in nature, occupying the

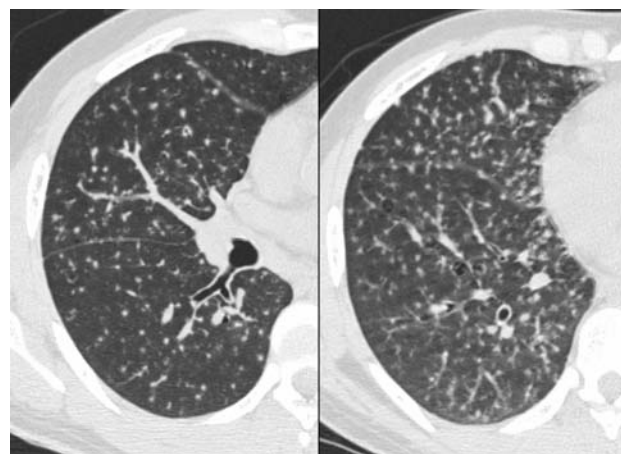


Figure 63 Random nodules seen on 1-mm HRCT images. Note the contact of nodules along the major and minor fissures and along the subpleural surfaces. However, there are many other nodules that do not appear related to these structures, attesting to the random distribution. In this case the relatively homogeneously small nodules were due to miliary tuberculosis. *Abbreviation:* HRCT, high-resolution technique.

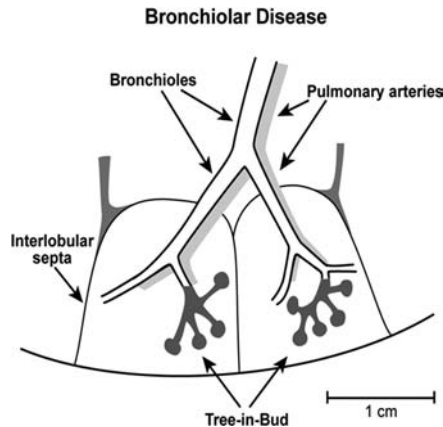


Figure 64 Nodules spare the interlobular septa and pleural surfaces confirming a centrilobular nature. There are both clusters of nodules and others with a more clearly arborizing nature termed tree-in-bud. These specific findings are indicative of airways disease. *Source:* From Ref. 476.

intermediate space between the core structures of the secondary pulmonary lobule and the periphery of the secondary pulmonary lobule (480,481). If a centrilobular nodular distribution is patchy and associated with clusters of nodules or nodules in a tree-in-bud distribution, the pattern indicates the presence of bronchiolar disease (Fig. 64). In these cases the nodules reflect focal impaction of tiny side-branch airways and alveoli surrounding the stem of the core terminal bronchus—a finding indicative of infectious bronchiolitis (Fig. 65) (344,369,482). In patients with centrilobular nodules but no clustering or tree-in-bud pattern, the nodules are more likely to be diffuse and ground glass in density (Fig. 66). In these cases the nodules are often upper lobe predominant and may be caused either by subacute hypersensitivity pneumonitis (Fig. 67) (17,483–485). The main differentiation between these two entities relies on the clinical setting, as respiratory bronchiolitis is a smoking-related illness. Additionally, smokers appear to be less likely to be affected by hypersensitivity pneumonitis. Patients with respiratory bronchiolitis typically present with cough and dyspnea and have mixed restrictive and obstructive pulmonary function tests. Respiratory bronchiolitis is part of the spectrum of smoking-related diseases that include respiratory bronchiolitis-interstitial lung disease (RB-ILD) and desquamative interstitial pneumonitis (DIP). The appearances may therefore coexist with evidence of emphysema and bronchial wall thickening indicative of smoking-related bronchitis. When RB progresses to RB-ILD, confluent areas of ground-glass density correlate with pigment-laden macrophage infiltrate in the respiratory bronchioles and the adjacent alveoli.

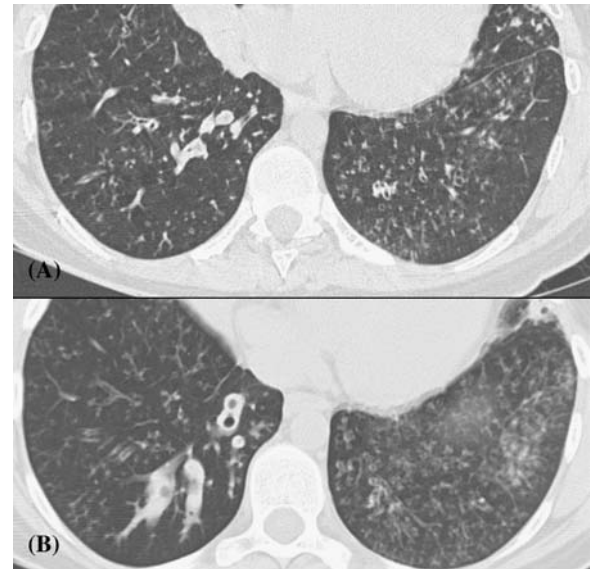


Figure 65 Bronchiolar disease. (A) One-millimeter HRCT section. (B) Five-millimeter HRCT section. Bronchiectasis with mucoid impaction and small airways disease. Note the tree-in-bud opacity in the left lower lobe indicating bronchiolar disease, in this case due to concurrent active small airway infection. On occasion the tree-in-bud opacity may be easier to characterize on slightly thicker sections (3–5 mm) compared with the HRCT 1-mm images as more of the airway anatomy is visualized to allow anatomic correlation of the nodules to the airways. *Abbreviation:* HRCT, high-resolution technique.

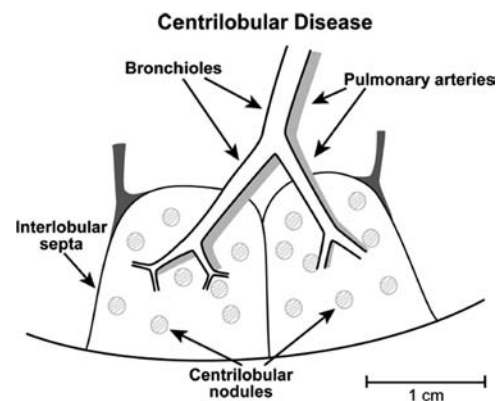


Figure 66 Nodules spare the interlobular septa and pleural surfaces confirming a centrilobular nature. The nodules are diffuse and ground glass in nature without evidence of clustered nodules or tree-in-bud opacities. The findings will likely reflect hypersensitivity pneumonitis or respiratory bronchiolitis. *Source:* From Ref. 476.

The use of the above anatomic-based algorithm has been demonstrated to be associated with a high degree of accuracy (94%) and interobserver concurrence in the diagnosis of multinodular disease.



Figure 67 One-millimeter HRCT image shows centrilobular ground-glass nodules. A diffuse carpeting of small ground-glass nodules is present. Because of the extent of nodules the micro-anatomic location can be difficult to establish; however, in this case the absence of nodules adjacent to the fissures or pleura casts a black “rim” around the nodules indicating their centrilobular distribution. The etiology was hypersensitivity pneumonitis in this patient with a history of multiple bird pets. Respiratory bronchiolitis due to heavy smoking can appear indistinguishable. *Abbreviation:* HRCT, high-resolution technique.

Reticular Opacities

Reticular, also termed linear, opacities are characterized by the presence of small discrete linear abnormalities that may be assessed as either interlobular or intralobular. When there are extensive intralobular septations, reticular densities that are oriented predominantly in the axial plane may appear as ground-glass density due to partial volume averaging with air within the same voxel. Therefore, the presence of ground-glass density in a patient with diffuse reticular disease does not necessarily imply the presence of airspace disease or alveolitis.

When reticular disease is present, one of the foremost considerations for CT diagnosis is the determination of accompanying fibrosis. Fibrosis may be implied if there is architectural distortion of the vascular structures, tractional bronchiectasis, or, in more pronounced cases, signs of greater volume loss such as fissural displacement, diaphragmatic elevation, or shift of the hilar structures.

Reticular opacities without fibrosis

In the absence of fibrosis, reticular markings are most often related to interstitial edema. The diagnosis is supported by prominent interlobular septa with ancillary findings such as cardiomegaly, dilatation of the venous vasculature, patchy perihilar ground-glass density, or effusions. In edema, interlobular septal thickening is usually bilateral and symmetric, although asymmetry may occur because of prolonged dependence on one side. When asymmetric and located distal to a mass, the diagnostic task shifts to differentiating between benign postobstructive lymphedema and lymphangitis carcinomatosa. Smooth interlobu-

lar or intralobular septal thickening distal to a mass is usually secondary to postobstructive lymphedema (Fig. 61). A similar appearance may also be seen distal to a pneumonic consolidation without a mass. Lymphangitic carcinomatosa is occasionally associated with smooth interlobular septal thickening but far less commonly than the more typical nodular septal thickening. It must be also noted that the suggestion of a diagnosis of lymphangitic carcinomatosa based upon the CT appearance of smooth interlobular septal thickening may deny an attempt of curative intent therapy and should be supported by other PET findings.

Interlobular and intralobular septal thickening may occasionally occur in the absence of findings of fibrosis but in combination with airspace disease and ground-glass density. As many parenchymal airspace processes resolve, they may become more reticular in nature. For example, consolidation due to pneumonia or COP (Fig. 68) or ground-glass density related to *Pneumocystis carinii* (PCP) or hemorrhage tends to become more reticular during subacute organizational or resolving phases (Fig. 68) (486–488). The presence of some accompanying mild retractile change of the lung parenchyma is frequently helpful in distinguishing these benign etiologies from lymphangitic disease. True combined reticular and airspace disease without any apparent fibrosis may occur during an early alveolitis or in a diffuse infiltrative disorder such as alveolar proteinosis. The latter entity, a disease in which there is abnormal alveolar accumulation of PAS-positive material, is characterized by the presence of a combination of symmetrically distributed perihilar ground-glass and inter- and intralobular septal thickening, an appearance termed “crazy-paving” (Fig. 68) (489–491). The disease is typically primary, although increasingly a secondary version is appreciated in patients with a known malignancy.

Reticular opacities with fibrosis

These abnormalities are best classified according to the distribution of radiological findings. Reticular opacities when patchy, limited, or focal may reflect the sequela of remote postinflammatory or infectious episodes. Typically, e.g., postgranulomatous scarring will occur in the posterior lung apices (Fig. 44). Radiation fibrosis in the apices from prior mediastinal irradiation, conversely, is more medial and paramediastinal in nature. Findings of bilateral and diffuse fibrosis are more suggestive of a diffuse interstitial pulmonary fibrosis. Differentiation of the types of interstitial fibrosis may be challenging and is aided by the use of HRCT images. Fibrosis may be suggested even on the lower resolution CT scans obtained for routine PET/CT. In this regards, the availability of a coronal rendered volume of HRCT images may provide added diagnostic value by aiding the interpretation of the

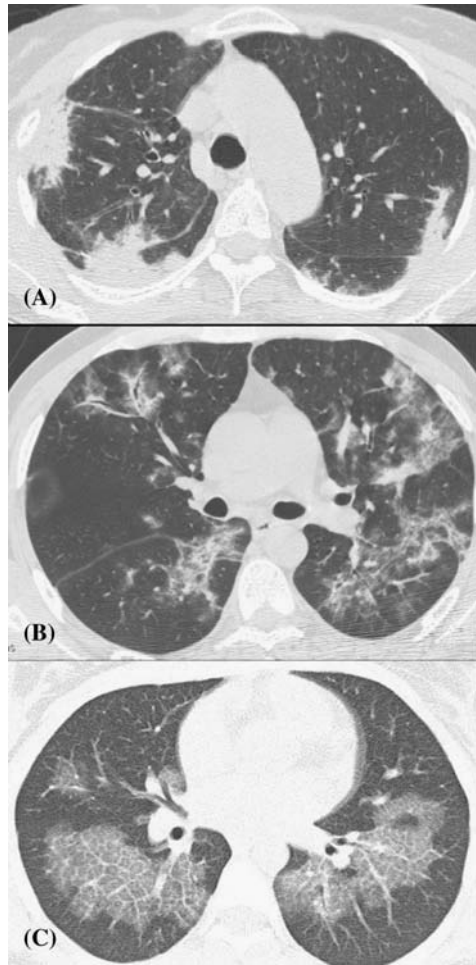


Figure 68 (A) Cryptogenic organizing pneumonia—5-mm CT section. This entity formerly was known as BOOP; as bronchiolitis obliterans is not a dominant feature, the former nomenclature was abandoned. In cases of chronic infection or other known predisposing factor the term organizing pneumonia is used. In the frequent case of idiopathic OP the term COP is now correct. Typically peripheral areas of chronic airspace consolidation, are associated with mild areas of tractional bronchiectasis. Biopsy may be required to differentiate from other causes of chronic parenchymal consolidation such as bronchioalveolar cell carcinoma. (B) Subacute PCP infection. Parenchymal ground-glass and consolidative opacity, reticular change, and minor retractile change of the parenchyma is present without significant fibrosis and should not be confused for interstitial fibrosis. (C) “crazy-paving” appearance 1-mm HRCT image. Ground-glass opacity combined with intra- and interlobular septal thickening result in this appearance that when diffuse and perihilar is rather typical of pulmonary alveolar proteinosis. Appearance has been described in many other entities although rarely as diffuse. *Abbreviations:* COP, cryptogenic organizing pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; OP, organizing pneumonia.

disease distribution. Moreover, many of these processes when they are active will demonstrate FDG uptake, more often curvilinear and peripheral in pattern than nodular or mass-like (15). The most commonly encountered interstitial fibrosis patterns are described below.

Usual interstitial pneumonitis. The most frequently encountered pattern of interstitial fibrosis. Usual interstitial pneumonitis (UIP) can be diagnosed with a high degree of specificity based upon HRCT findings (492–494). UIP-pattern fibrosis is characterized by the presence of predominantly peripheral, basilar and subpleural reticular intralobular and interlobular septal thickening, and areas of tractional bronchiectasis or lung retraction (Fig. 69). The disease process may appear mild in some regions but advanced with areas of honeycombing in others. This feature is termed temporal and spatial heterogeneity and is in contradistinction to the temporal and regional homogeneity of disease processes such as DIP. This difference implies that UIP may be a result of long-term repetitive lung injury as opposed to a singular lung insult in DIP (495–497).

The etiology of UIP-type fibrosis is variable and may reflect the sequela of a wide variety of clinical diseases including asbestosis, connective tissue disorders, or drug toxicities (in particular methotrexate, bleomycin, and amiodarone). In the absence of a clinical history or radiological findings supportive of these precipitants, the commonest etiology is idiopathic pulmonary fibrosis. The presence of honeycombing in UIP is a factor of great significance, as this infers a much worse prognosis and shorter life expectancy. UIP fibrosis in its early phase may be limited to the posterior lung bases. This is particularly

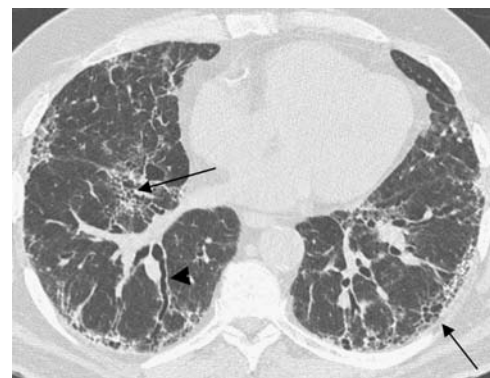


Figure 69 One-millimeter HRCT image shows usual interstitial pneumonitis-idiopathic pulmonary fibrosis. Note the predominantly peripheral distribution of reticular opacities associated with features of pulmonary architectural distortion, in this case the presence of honeycombing (long arrow) and tractional bronchiectasis (arrowhead). This disease process is usually symmetric, with areas of heterogeneity in the extent of fibrosis. The posterior lung bases are almost ubiquitously affected.

the case in patients with asbestosis. In these patients, the earliest features are often minimal reticular change and ground glass in the posterior lung. Given these appearances may be mimicked by dependent atelectasis, particularly if the patient has been supine for a period of time, limited prone HRCT imaging may be beneficial by eliminating dependent changes in patients in whom there is a high clinical suspicion for fibrosis. FDG uptake in UIP is seen (Fig. 18) (498). The nodules associated with UIP will be active.

Non-specific interstitial pneumonitis. A confident CT diagnosis of nonspecific interstitial pneumonitis (NSIP) is far less frequently made in comparison with UIP. In addition, the diagnosis on histopathology has been subject to varying criteria, and therefore interobserver disagreement is also substantial. The histological classification is confounded further by the presence of sampling errors in biopsies of the lung parenchyma (494,499–501). The commonest feature of NSIP is the presence of ground-glass attenuation that is usually lower-lobe predominant and symmetric (Fig. 70).

Like UIP, NSIP is associated with connective tissue disorders. It is currently believed that NSIP may be more commonly associated with mixed connective-tissue disease (MCTD) rather than UIP (502–504). NSIP is less rapidly progressive and may explain the historical longer-term survival of patients with MCTD and fibrosis, which was initially classified as UIP but may indeed have been NSIP. The diagnosis of NSIP is, therefore, aided by a clinical suspicion based on a history of MCTD. Factors that are suggestive of the presence of NSIP include a pattern predominantly comprising ground glass with minimal if any honeycombing. The ground-glass process may be diffuse or peribronchial and typically involves a greater portion of the central lung parenchyma than UIP. Occasionally focal areas of subpleural sparing of disease are demonstrated.

Desquamative interstitial pneumonitis. DIP is part of the spectrum of smoking-related diseases that includes RB and RB-ILD. DIP is typified by the presence of pigment-laden macrophages infiltrates resulting in geographic areas of ground-glass attenuation with only minimal reticular change and minor fibrosis (17,505). The disease may superficially mimic heterogeneous lung attenuation secondary to airway disease, particularly as there may be accompanying airway thickening (Fig. 71). However, unlike genuine airways disease the heterogeneous lung attenuation pattern does not become accentuated in expiration. DIP has a relatively benign course without significant progression to fibrosis (506,507). Its appearance on FDG PET has not been reported.

Chronic hypersensitivity pneumonitis. Chronic hypersensitivity pneumonitis results from progression from the subacute phase and reflects a long-standing exposure to



Figure 70 (A) Nonspecific interstitial pneumonitis (NSIP). One-millimeter HRCT image shows diffuse parenchymal ground glass present. However, the airways in the lower lobes indicate that the process is mildly fibrotic, causing tractional airway dilatation. However, as in most cases of NSIP, honeycombing is conspicuously absent. The esophagus is dilated and patulous in this case, revealing the underlying connective tissue disorder of scleroderma. (B,C) Two coronal slices from an FDG PET in a patient with scleroderma show peripheral lung activity in the nonspecific interstitial pneumonitis. *Abbreviation:* HRCT, high-resolution technique.

inhaled organic antigens that incite an inflammatory response. Chronic hypersensitivity pneumonitis is associated with diffuse patchy bronchial wall thickening, ground-glass opacity, and reticular changes. A slight basilar predominance is described; however, the disease tends to involve the entire lung (508–510). The disease reflects inflammation to airborne material, and certain segmental airways may become inflamed, while others are spared. In this fashion, fibrosis and ground-glass density may be prominent in one lobule but entirely absent in adjacent lobule. Additionally, decreased areas of perfusion related to air trapping may occur. This heterogeneity of findings is typical of chronic hypersensitivity pneumonitis and has been termed the “head-cheese sign” (Fig. 72). As might be expected, expiratory imaging



Figure 71 Desquamative interstitial pneumonitis. One-millimeter HRCT image shows a uniform homogenous alveolar macrophage infiltration results in a lobular distribution of ground-glass density with little or no fibrosis. There may be minimal reticulation or fibrosis. Bronchial wall thickening is often present reflecting the smoking-related nature of this disease. *Abbreviation:* HRCT, high-resolution technique.



Figure 72 Chronic Hypersensitivity Pneumonitis. One-millimeter HRCT image shows reticular and ground-glass opacity in a markedly heterogenous distribution with areas of lobular sparing, which in combination with areas of low attenuation related to air-trapping create the so-called head-cheese appearance. The distribution is often segmental with airway thickening in the affected segments. Although the appearances are often basilar predominant, there are many cases of diffuse and upper lobe disease described. *Abbreviation:* HRCT, high-resolution technique.

accentuates the differences in lung attenuation in the lung parenchyma (483,485,509,511,512). In most cases, the etiology of the hypersensitivity will be unknown. However, significant improvement with or without removal of an identified environmental antigen can often be achieved with steroid therapy (513,514).

Increased Lung Density—Consolidation and Ground-Glass Opacity

Increased lung density generally results from either parenchymal airspace consolidation or parenchymal ground-glass density. Undoubtedly, the most common cause for focal or multifocal airspace consolidation is infection. Infection can have a variable appearance on CT imaging. Most characteristically, infection will present as ill-defined parenchymal opacities, containing air-bronchograms, tending to coalesce into larger areas of parenchymal consolidation that may be sublobar, lobar, or multilobar. The distribution of disease may be extremely variable, appearing unilateral, bilateral, central, or peripheral. Clustered centrilobular nodules or tree-in-bud opacities indicative of bronchiolitis are often detected at the periphery of areas of consolidation (Figs. 44,65) and should increase diagnostic confidence for infection. Infective bronchiolitis is not ubiquitous in infection and had previously been thought to be relatively characteristic of mycobacterial disease. Although it is more common in endobronchial mycobacterial infection, bronchiolitis is now appreciated to be relatively nonspecific.

Although different pathogenic organisms have a propensity for particular locations, e.g., reactivation tuberculosis in the upper lobes, these patterns are rarely sufficiently specific for a confident specific microbiological diagnosis. Even in tuberculosis, variability is the norm, particularly in immune-compromised hosts in whom distribution of disease is frequently atypical. Additionally, other findings may also be noncontributory. For example, cavitation is a feature characteristically associated with staphylococcal or anaerobic infections, but is relatively frequently seen even in *Streptococcus pneumoniae* infections because of the high incidence of *Streptococcal pneumonia* overall. Nonetheless, the distribution and appearances of parenchymal airspace disease may raise clinical consideration of more specific diagnosis. For example, the presence of airspace disease at the lung bases and in the dependent portions of the lung, even in the absence of cavitation, may be indicative of aspiration and infection with anaerobic or gram-negative organisms.

A frequent consideration in a patient with extensive parenchymal consolidation is whether there is proximal neoplastic airway occlusion. Therefore, a careful review of the airways leading to atelectatic or consolidated areas of the lung parenchyma is essential. The detection of a mass lesion central to, pleural effusion adjacent to, or cavitation within the consolidated lung parenchyma is greatly aided by the acquisition of CT after the administration of intravenous contrast. The enhancement of a central venous mass is often less intense and more delayed compared with the more peripheral atelectatic parenchyma, within which a lesion can be concealed on

noncontrast images. However, the presence of infective or noninfectious pneumonitis may lower the enhancement of the peripheral lung. PET imaging may be of particular value in this regard as it is often able to depict the central higher biological activity of a neoplastic mass (Fig. 40).

In the absence of bronchiolitis, the diagnosis of pneumonia based upon parenchymal consolidation or ground-glass density requires clinical corroboration to exclude other common causes of airspace disease that mimic or coexist with infection. For example, the presence of engorged venous vasculature, basilar interlobular septal thickening, and effusions should suggest edema; however, it must be recalled that both septal thickening and effusions may occasionally occur in the periphery of areas of infective consolidation as a result of mild lymphedema. Additionally, edema is frequently unilateral in debilitated patients, affecting the dependent side.

Although acute pulmonary edema may occasionally present with patchy perihilar parenchymal ground-glass density and no other supportive features, such an appearance raises the possibility of opportunistic infection, particularly if the patient is known to be immune compromised. This pattern is most commonly seen in infection with PCP; however, other viral organisms including cytomegalovirus may appear similar. PCP infection may be cyst forming and tends to heal with retraction and increasing prominence of the interlobular septa. The airways in the region of infection may demonstrate mild transient dilatation indicative of tractional change. On FDG PET, activity may be expected in any of these entities and has been specifically reported in PCP (515,516), bacterial pneumonias (Fig. 73) (517,518), lung abscesses (519), and viral pneumonia (520). Mycobacterial infections are especially FDG-avid (340).

Other considerations for acute diffuse consolidative or ground-glass opacity include diseases with the end-result of diffuse alveolar damage, whether these are secondary to known pathologies as in acute respiratory distress syndrome or idiopathic as in acute interstitial pneumonitis. Diffuse pulmonary uptake of FDG has been described on PET (521), and the intensity of uptake appears to correlate with neutrophil activation that occurs in acute lung injury (522). Pulmonary hemorrhage and acute drug toxicities may cause similar appearances by combinations of hemorrhage, diffuse pneumonitis, diffuse alveolar damage, or acute eosinophilia.

Less common etiologies of focal parenchymal consolidation or ground-glass attenuation may be suggested by distribution (e.g., peripheral upper lobes in chronic eosinophilia), symptoms (e.g., hemoptysis in parenchymal hemorrhage), chronicity (e.g., organizing pneumonia, bronchioloalveolar cell carcinoma, lymphoma, and alveolar proteinosis), or laboratory correlation (acute and chronic eosinophilia) (160,341,523–525).

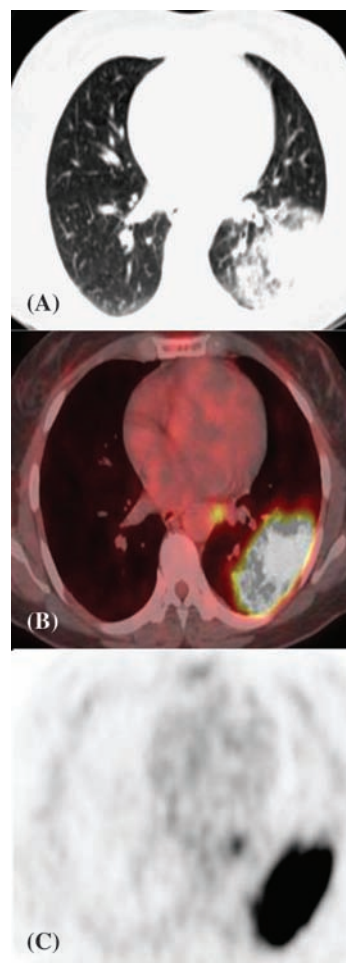


Figure 73 Community acquired pneumonia: an asymptomatic 54-year-old woman who had a left lower lobe density on routine chest X ray. A diagnostic CT showed a rounded mass-like soft tissue density without air bronchograms surrounded by ground-glass opacity, and malignancy could not be excluded. PET/CT performed three days later showed a more extensive (A) infiltrate on CT that fused (B) to an area of metabolic activity on PET (C). The patient was scheduled for biopsy. She developed a fever and began producing sputum two days after the PET/CT scan. Sputum was positive for pneumococcal pneumonia. With antibiotics, she defervesced, and the consolidation resolved consistent with a “round” pneumonia.

Reduced Lung Density—Emphysema, Asthma, Airways Disease, and Air Trapping

Emphysema

Permanently reduced lung density may be the result of irreversible lung destruction by emphysema. Upper lobe predominant centrilobular emphysema and paraseptal emphysema are the commonest appearances of smoking-related COPD. Panacinar emphysema is rapidly progressive,

occurs in young patients with alpha1-antitrypsin deficiency, and is basilar predominant.

Reduced lung density also occurs without irreversible lung destruction when the lung becomes hyperinflated, most typically due to air trapping related to small airway inflammation. Such appearances are frequent in both asthmatics and patients with COPD. Factors suggestive of airway inflammation include the demonstration of bronchial wall thickening in larger bronchi and bronchioles. However, full imaging assessment of air trapping usually requires the performance of expiratory HRCT to demonstrate lobular or subsegmental air trapping. In general, CT is insensitive to the detection of exacerbations of asthma or COPD and may only detect surrogates of the disease such as increased bronchial wall thickening or concurrent infections or complications such as pneumothorax or pneumomediastinum.

Bronchiectasis

Patients with dilated non-tapering airways in the absence of an acute infective episode are considered to have bronchiectasis. These patients will frequently also have air trapping on CT but likely will also suffer from recurrent episodes of airway impaction and airspace infection. Remarkably, there are no widely acceptable diagnostic criteria for the diagnosis of bronchiectasis. This is less important in gross cases of saccular or cystic bronchiectasis but more problematic in patients with borderline cylindrical bronchiectasis. A reasonable but not universally accepted criterion suggests that in evaluation of similar generation airways and accompanying arteries using HRCT the overall diameter of the airway should not be greater than 25% larger than the accompanying artery. It is also probably safe to suggest bronchiectasis when a bronchus is visualized within 1 cm of the costal pleura or in contact with the mediastinal pleura (526,527). Even more remarkable than

the lack of standardized criteria for the detection and diagnosis of bronchiectasis is the absence of criteria for staging the extent and severity of disease. The Bhalla criteria have been developed for cystic fibrosis (CF) but have limited applicability to etiologies with less severe bronchiectasis (528). Evaluation of bronchiectasis exacerbations by PET may be a useful indicator of disease activity that may guide treatment (Fig. 74).

Cystic fibrosis

CF is characterized by increasing airway obstruction, persistent infection, and neutrophilic inflammation (Fig. 75). Bronchioloalveolar lavage (BAL) is the gold standard for assessing airway inflammation; however, the procedure is invasive, and the lung segments that are sampled may not accurately represent the entire lung involvement.

To quantify the efficacy of antiinflammatory agents in patients with CF, a measure of lung function (usually FEV1) is most commonly used (529). However, the use of FEV1 has been criticized since it does not always correlate with the changes of local inflammatory activity (530–532). Noninvasive “anatomic” imaging methods (chest radiographs or CT) identify the extent of changes in the lungs but do not easily quantify disease activity. FDG PET can be useful in patients with CF. The rate of FDG uptake is greater than in normal volunteers and is especially increased in the group of patients with the most accelerated rates of deterioration in pulmonary function. The rate of uptake of ^{18}F FDG by the lungs of patients with CF correlated with the number of neutrophils in the BAL fluid. There is, however, regional variation in the lung uptake of ^{18}F FDG in CF patients, with increased uptake in the upper lung zones (533). This regional uptake is consistent with prior studies using chest CT that showed more disease in the upper lung zones (534). The ability of FDG PET to identify and quantify regional pulmonary

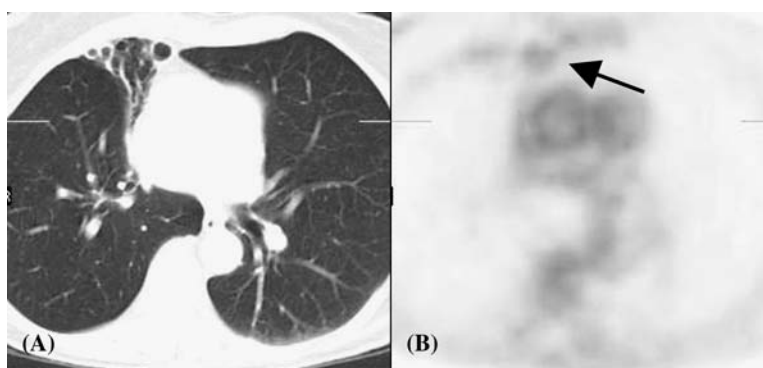


Figure 74 This patient underwent a PET/CT for surveillance for a past history of lymphoma. The CT scan (A) shows bronchiectasis in the right middle lobe. The corresponding PET scan (B) shows mild uptake (arrow) that fused to the medial cyst consistent with inflammation.

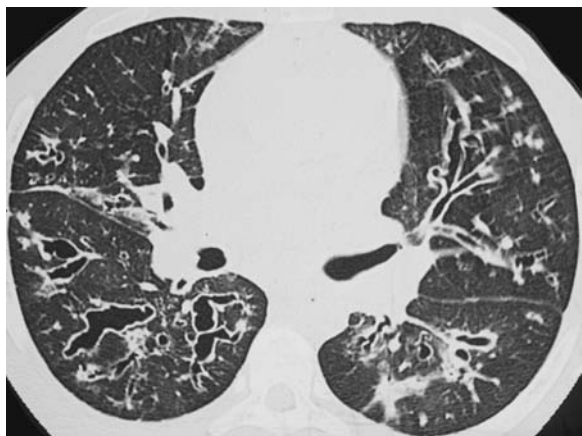


Figure 75 Cystic fibrosis. A 1-mm HRCT section shows bilateral, diffuse, and marked bronchiectasis associated with multiple areas of mucoid impaction and focal parenchymal inflammation. Despite its name the morphology of bronchiectasis can be quite variable in CF including cylindrical, varicose, and cystic changes. *Abbreviation:* CF, cystic fibrosis; HRCT, high-resolution technique.

inflammation may allow a more precise monitoring of airway inflammation (533).

Inhomogeneous Lung Attenuation and Mosaic Lung Attenuation

Inhomogeneous lung attenuation is applied when there are heterogeneities in the lung attenuation and has also been termed a mosaic pattern when present. Inhomogeneous lung attenuation may occur secondary to the presence of ground-glass attenuation, a decrease in blood flow, or a combination of the two. The term mosaic perfusion can be applied on CT when decreased blood flow is felt to be the cause of inhomogeneous lung opacity. In mosaic perfusion, areas of lung attenuation appear lower than others and contain vessels that are decreased in terms of size and possibly number. Decreased perfusion of the lower attenuation areas is related in a majority of cases to air-trapping which leads to reflux vasoconstriction, with the remainder of cases related to vascular obstruction or a mixture of the two processes. Chronic thromboembolic disease is the major cause of vascular obstruction associated with mosaic perfusion. The term mosaic attenuation is more general and utilized when decreased vascular size cannot be confirmed.

When the vasculature is not attenuated in the lower attenuation areas of the lung parenchyma, ground-glass opacity is the likely cause of the inhomogeneous lung. A combination of mosaic perfusion, ground-glass attenuation, and normal lung, as mentioned before, can lead to the head-cheese sign.

PLEURAL DISEASE

Malignant Pleural Disease

Several anatomic imaging modalities have been used to evaluate noninvasively pleural disorders. CT is considered is a useful modality for assessing the pleura. However, CT cannot differentiate many infectious disorders from pleural malignancies and pleural fibrotic change from active malignant diseases. Assessment of suspected pleural disease, whether malignant or benign, using CT is best performed with the administration of intravenous contrast. Use of this technique maximizes the ability to differentiate the adjacent lung parenchyma from the pleural process; identify the presence of accompanying pleural thickening or nodularity; and reveal any areas of loculation (Fig. 76). MRI has been shown to be of value in assessing for chest wall and extrapleural involvement of malignant pleural disease.

Metastatic Pleural Disease

Secondary malignancies that typically involve the pleura are most typically adenocarcinomas including lung cancer, breast carcinoma, gastric carcinoma, and ovarian malignancies. A small proportion of metastases occur due to drop metastases from invasive thymoma or lymphoma.

Differentiation between benign and malignant effusions is important since resectability is excluded in the case of a malignant pleural effusion. A pleural effusion on CT with areas of focal soft tissue density or diffuse soft tissue thickening, particularly greater than 1 cm, raises suspicion of the presence of malignant pleural disease (535,536). Circumferential pleural thickening involving

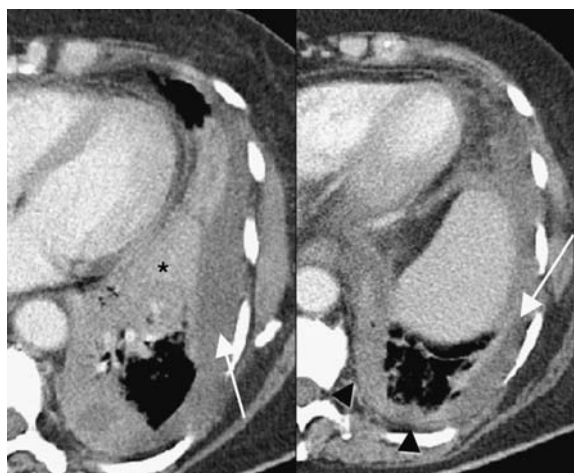


Figure 76 Lung carcinoma with malignant effusion. Benefit of contrast administration. Intravenous contrast administration helps to differentiate atelectatic lung parenchyma (asterisk) from loculations of pleural fluid (long arrows), and basilar pleural thickening (arrowheads).

the entire perimeter of a hemothorax is also very suggestive of malignant involvement of the pleura (Fig. 77).

Pleural effusions without demonstrable thickening are not infrequently (537) malignant (536). Thus, given the low sensitivity and specificity of CT, cytologic analysis of the fluid is typically performed. Fluid cytologic analysis after thoracentesis has been reported to be positive in only 66% of malignant pleural effusions for NSCLC. Pleural biopsy may therefore be needed to confirm the diagnosis of malignancy, although investigation has demonstrated even low sensitivity for malignancy using this technique. In 25% of patients in whom a diagnosis of etiology for an effusion could not be established at pleural biopsy, a malignant diagnosis was

made 12 days to 6 years after thoracotomy and included lymphoma, carcinoma, and mesothelioma (538). Malignant pleural disease may appear on CT as multiple focal nodules or nodular pleural thickening without accompanying pleural effusion. The presence of small nodular densities aligned along the fissural surfaces raises suspicion of malignant “pleural studding” (Fig. 77).

PET AND METASTATIC PLEURAL DISEASE

Pleural effusions are found in one-third of patients with NSCLC at the time of presentation. Those with effusions that are cytologically or pathologically proven to be malignant are given a tumor descriptor of T4 and, hence, a stage designation of stage IIIB. 18F-FDG PET has been used to evaluate pleural fluid and pleural masses for evidence of malignancy (539–542).

Evaluating 25 patients with NSCLC and suspected malignant pleural effusions, Erasmus et al. reported a very high positive predictive value of 95% for FDG PET (543). Including a larger number of benign pleural effusions, a later study on 92 patients compared 18F-FDG PET with CT in the differentiation of benign from malignant pleural effusions. Sensitivity, specificity, positive predictive value, and negative predictive value of FDG PET were 100%, 71%, 63%, and 100%, respectively (544), that became 100%, 76%, 67%, 100%, respectively, when CT and FDG PET were combined. The negative predictive value was 100%, suggesting that a negative FDG PET scan and an indeterminate pleural abnormality on CT usually indicate a benign process. Similar results were seen in another study including 98 patients by Duysinx et al.: sensitivity and specificity of PET in identifying malignancy were 96.8% and 88.5%, respectively, with a positive and negative predictive value of 93.8% and 93.9%, respectively (545). In another report, FDG PET images showed true direct extension of activity into the pleura from the primary lung lesion in nine patients, while the CT scan was positive in only three patients (8).

These data indicate that FDG PET is able to accurately characterize pleural effusion when extension to the pleura of primary pulmonary malignancy is suspected. This may be particularly important after equivocal findings on CT or negative results from pleural cytology after thoracentesis and might reduce the number of open pleural biopsies and thoracotomies performed for benign pleural disease. PET/CT hybrid systems have the capability to increase the specificity of FDG PET imaging in types of pleural lesions, but data on this matter are still lacking.

Malignant Pleural Mesothelioma

Exposure to asbestos can lead to chronic inflammatory pleural reaction resulting in thickening and fibrosis.

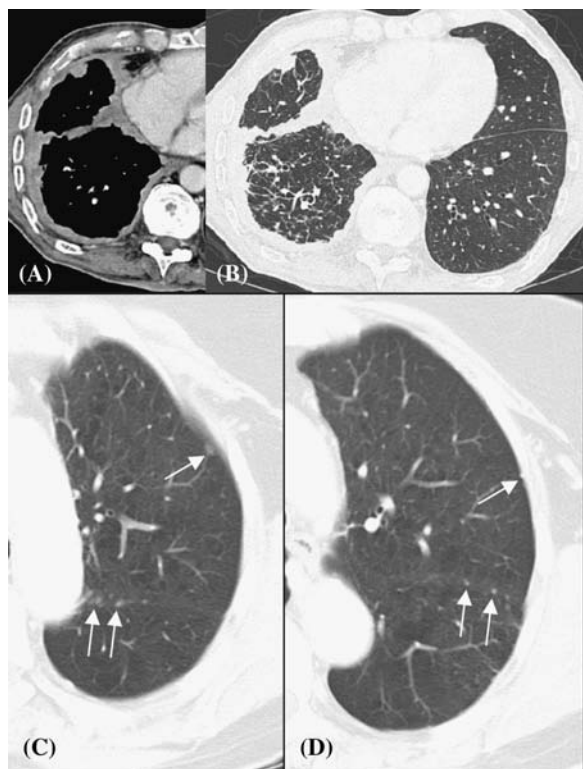


Figure 77 Malignant pleural disease, metastatic adenocarcinoma. Mediastinal (A) and lung windows (B), following intravenous contrast, 5 mm sections. Complete encasement of a hemithorax by nodular pleural thickening is a feature of malignant disease. In this case involvement of the visceral pleural surfaces is confirmed by the major fissure thickening. Thickening of the interlobular septa is present at the right lung base. This may be secondary to hilar lymphatic obstruction or lymphangitic carcinomatosis, which may coexist in pleural malignancy. (C–D) Pleural metastases. Pleural studding (arrows) in another patient with a left lower adenocarcinoma (not shown). These nodules were absent six months previously. The development of new small nodules in a patient with a known or suspected malignancy requires short-term follow-up to exclude metastatic disease. In this case metastases were suspected in view of the distribution and confirmed at VATS.

Asbestos exposure in combination with a smoking history is associated with a very high risk for mesothelioma. Typically, approximately 35 to 40 years pass between onset of exposure and development of mesothelioma (546). Not surprisingly therefore, the incidence of mesothelioma is expected to continue to increase in the ensuing next decade despite increasing awareness and precautions pertaining to asbestos exposure (547). Mesothelioma however in approximately 10% of cases occurs in individuals without significant asbestos history (548). Malignant pleural mesothelioma (MPM) carries a poor prognosis: current median survival after diagnosis is between 12 and 18 months. Early diagnosis and aggressive surgical treatment can significantly improve long-term survival. Diagnosis is currently made by thoracoscopic biopsy, since

cytologic examination of pleural fluid is positive only in about 25% of these cases.

Common CT findings associated with mesothelioma include a unilateral pleural effusion, nodular pleural thickening, interlobar fissure thickening, and tumor invasion of the chest wall, mediastinum, and diaphragm (Fig. 78) (549). The process frequently involves the circumference of the pleural surface when viewing in axial section. Associated involvement of the fissural surfaces is common. The pleural thickening in mesothelioma has been described to encase the involved hemithorax with resultant volume loss. Involvement of the mediastinal pleural with mesothelioma is not uncommon. The mediastinum tends to not shift away from the space-occupying pleural process but rather remains “fixed” in the midline,

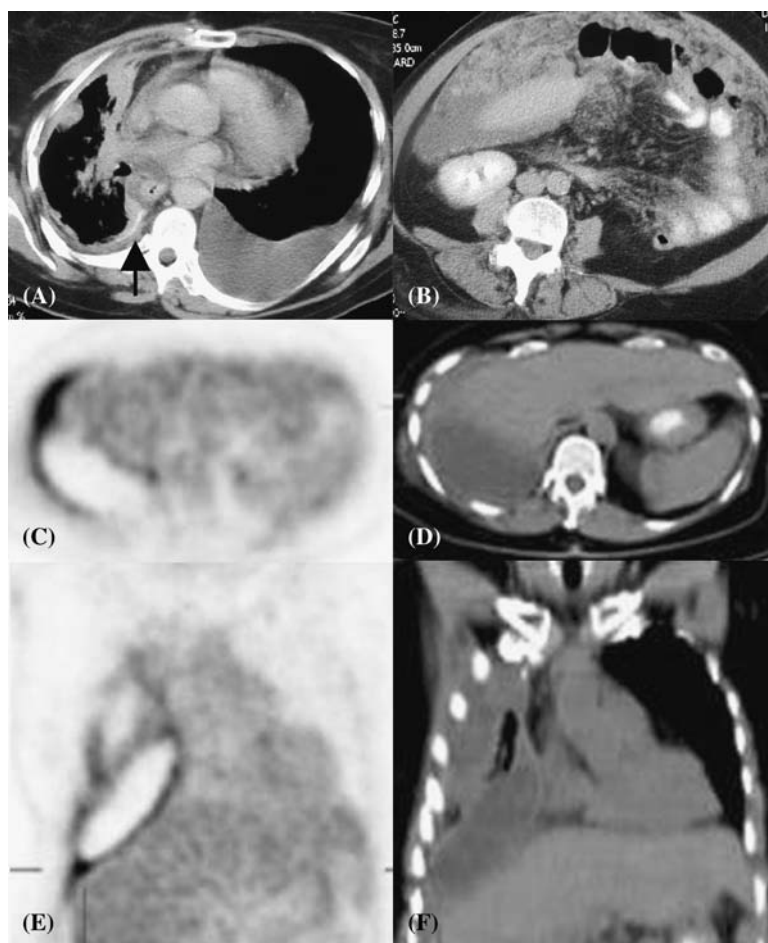


Figure 78 Pleural and peritoneal malignant mesothelioma. (A) The right hemithorax is encased and contracted in volume. Numerous more nodular foci of pleural disease are present. There is a small right effusion associated with posteromedial pleural calcification (*arrow*) attesting to the prior asbestos exposure. CT image (B) demonstrates invasion of the upper abdomen through the diaphragm with nodular thickening of the omentum and numerous enhancing nodular deposits highlighted by ascites in the subhepatic space. Another patient who underwent PET/CT (C–F) Transaxial PET (C) shows an increased rind of activity fusing to the thickened pleura on the corresponding noncontrast CT image (D). The coronal PET (E) and CT (F) better demonstrate the extent of disease. The loculated fluid is not metabolically active.

as the pleural disease is felt to restrict mediastinal motion. Signs that have been helpful for suggesting mesothelioma rather than metastatic disease include invasion of the extrapleural fat and chest wall with destruction of adjacent ribs given the tumor's propensity for local invasion. Enlargement of pericardial and diaphragmatic nodes in addition to subdiaphragmatic nodes are not infrequent.

Biopsy using thoracoscopic techniques is typically the method of diagnosis. Boutin et al. reported sensitivities for pleural fluid cytology and percutaneous needle biopsy in 26% and 21%, respectively, while thoracoscopic biopsy sensitivity was 98.4% (550).

The combination of CT with thoracoscopy is currently used for staging and restaging of the disease. Since CT has limited sensitivity in detecting the degree of mediastinal

lymph node involvement and of local tumor extension (551), other imaging techniques have been tested in the staging process of mesothelioma. MRI has been shown to be superior to CT for assessing invasion of the diaphragm and for identifying solitary areas of respectable foci or invasion of the endothoracic fascia (subpleural fat invasion) (552).

The system for staging mesothelioma proposed by the International Mesothelioma Staging Group (553) has been gaining acceptance (Table 14 and Table 15). T3 disease is potentially resectable, while T4 disease is considered technically unresectable.

PET Findings

PET imaging has also been used in the evaluation of MPM. A common pattern of FDG uptake is a linear area of intense

Table 14 TNM Staging of Malignant Mesothelioma Proposed by the International Mesothelioma Staging Group

T-Primary tumor

T1a	Tumor limited to ipsilateral parietal pleura, including mediastinal, and diaphragmatic pleura; No involvement of the visceral pleura
T1b	Tumor involving ipsilateral parietal, pleura, and diaphragmatic pleura Scattered foci of tumor also involving visceral pleura
T2	Tumor involving each ipsilateral pleural surface with at least one of the following features: • involvement of the diaphragmatic pleura • confluent visceral pleural tumor (including fissures) or extension of the tumor from visceral pleura into underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumor: Tumor involving all of ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral with at least one of the following features:) • involvement of the endothoracic fascia • extension into the mediastinal fat • solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall • nontransmural involvement of the pericardium
T4	Describes locally advanced technically unresectable tumor: Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features: • diffuse extension or multifocal masses of tumor in the chest wall with or without associated rib destruction • direct transdiaphragmatic extension of tumor to the peritoneum • direct extension of the tumor to the contralateral pleura • direct extension of tumor to one or more mediastinal organs • direct extension of tumor into the spine • tumor extending through the internal surface of the pericardium with or without pericardial effusion; or tumor involving the myocardium

N-Lymph nodes

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes

M-Metastases

Mx	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Source: From Ref. 553.

Table 15 Stage Descriptions for Malignant Pleural Mesothelioma.

Stage	Description
Stage I	
IA	T1aN0M0
IB	T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0
	Any N1M0
	Any N2M0
Stage IV	Any T4
	Any N3
	Any M1

activity surrounding the lungs (Fig 78) and corresponding to the areas of pleural proliferation (554,555). FDG PET has been demonstrated to have a role in identifying malignant disease in cases of doubtful CT findings, with a specificity as high as 100% on the basis of lesion's FDG-avidity, in correctly staging MPM extrathoracic and mediastinal nodal metastasis and in providing prognostic information (555–557).

PET imaging can play a role in the differentiation of T3 from T4 disease, aiding in decision for surgical versus nonsurgical management. Recently PET/CT was found helpful in the selection of patients with MPM for surgery (extrapleural pneumonectomy) by improving the accuracy of M staging (558). CT and MRI tend to understage mesothelioma. PET/CT can improve diagnosis of unresectable disease. Erasmus et al. reported the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT/PET to 67%, 93%, 86%, 82%, and 83%, respectively, for the presence of T4 disease. In this study, CT/PET detected extrathoracic metastases (M disease) in 24% of patients that were not suspected after conventional clinical and imaging assessment (558). In terms of nodal status, varying sensitivities have been reported. More recently, it has been suggested that PET/CT is not very sensitive for nodal disease, given the difficulty in differentiating tumor from nodal tissue (558–560).

In terms of SUV and prognosis, patients with tumors with an SUV of greater than 4 have a 3.3-fold greater risk of death (561). The slow-growing epithelioid subtype of MPM may appear less FDG-avid given its low mitotic rate, resulting in possible cause of false-negative findings on FDG PET. However, its low FDG uptake correlate with relatively better survival compared with the other MPM types (562). Documented causes of false-positive findings include infectious pleuritis, inflammation secondary to asbestos plaques, other benign inflammatory processes (e.g., tuberculosis, parapneumonic effusion, sarcoidosis, fungal infection), recent surgery, and radiotherapy. The degree of FDG uptake in these disorders at times may be elevated exceeding an SUV of 2.5 (39).

Benign Pleural Disease

Talc Pleurodesis

Talc pleurodesis has been widely employed in the management of recurrent pneumothoraces and pleural effusions. Talc mechanism of action relies on chronic inflammation in both visceral and parietal pleura with subsequent adhesion of the two pleural layers. Instillation may be via a chest tube, or more recently, via thoracoscopic techniques. Characteristic imaging findings with talc pleurodesis is the presence of high-density linear or nodular deposits in the pleura, typically in the posterobasal region (Fig. 79). The high-attenuation areas in the visceral and parietal pleural surfaces may be separated by pleural fluid. Talc deposits can involve the fissural surfaces with associated fissural thickening. Pleural thickening

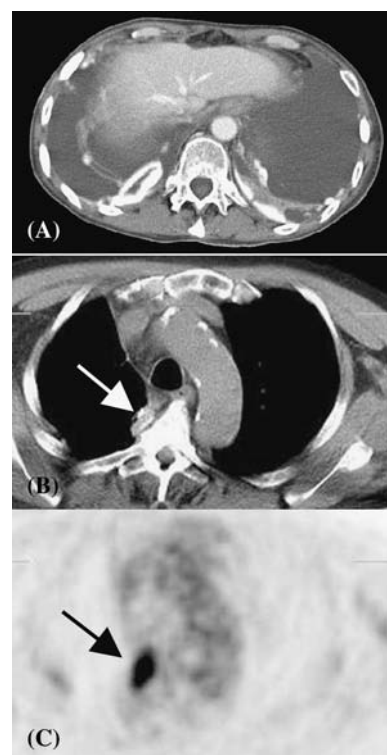


Figure 79 Talc pleurodesis. (A) The presence of high attenuation foci in the dependent pleural space is characteristic. On occasion these talc collections are difficult to differentiate from pleural calcifications. However, most typically, the foci of higher attenuation are a little less dense than calcium and may have ill-defined margins. They also typically reside in the dependent portions of the lung parenchyma and are less common but can occur in the anterosuperior thorax. (B–C) A PET/CT performed in a different patient who had undergone talc pleurodesis seven years before shows activity (arrow) on the PET (C) corresponding to the pleural talc (arrow) in the posteromedial right lung (B).

and nodularity with residual effusion are frequent (563,564).

On FDG imaging, moderate-to-intense plaque-like or focal nodular-increased uptake in the pleura on PET can be seen (Fig. 79) (565). Increased FDG activity is most often located along the surgically dependent area of the posteromedial pleura (565,566). The typical pattern of activity in talc pleurodesis-related inflammatory change is important to note to minimize unnecessary aggressive treatment or biopsy. The FDG uptake may be either diffuse or focal and may remain active and stable over a considerable period of time (565). Fused PET/CT images are particularly useful in cases with prior talc pleurodesis, since areas of intense FDG uptake can be correlated to high-attenuation areas representing talc granulomas on CT (567). New metastasis in the pleura on follow-up imaging may be seen as a new area of increased FDG uptake fusing to a new mass on CT. However, talc-related pleural masses may continue to demonstrate growth years after the pleurodesis (568), and it is conceivable that neither the degree of FDG uptake nor the evidence of proliferating tissue on CT may be able to differentiate talc pleurodesis from malignancy. Only tissue sampling in this scenario would help in deciding if a patient is to be followed expectantly rather than treated aggressively.

Pleural Effusions

Pleural effusions relating to benign entities are associated with numerous causes of infectious and inflammatory diseases. Effusions have been characterized as transudative or exudative. Transudative effusions are typically related to abnormalities in the balance between oncotic and hydrostatic pressure. Most commonly transudative pleural effusions are due to congestive heart failure, hepatic hydrothorax, and kidney disease. Exudative effusions relate to obstruction of lymphatic drainage or a change in capillary permeability. Exudative effusions can be caused by an extremely large number of entities; however, they are most frequently related to malignancy, infection, and pulmonary embolism (569). Collagen vascular disease, lymphatic disease, drugs, trauma, asbestos, and other nonspecific inflammatory etiologies are also etiologies (570). Quantitative criteria have been established by Light et al. for differentiating transudative and exudative effusions and involve the measurement of pleural fluid to serum ratios of LDH and total protein, a topic that is beyond the scope of this manuscript (571).

An exudative effusion that accompanies pneumonia has been termed a parapneumonic effusion. Clinically, an effusion is termed a complicated parapneumonic effusion when quantitative criteria involving pleural LDH, pH, and glucose levels are satisfied. The term empyema is utilized only when organisms are cultured out from the pleural fluid.

On CT imaging, transudative pleural effusions have fluid attenuation and are typically positioned in the dependent regions of the thorax in a meniscoid configuration. Focal contour abnormalities in the interface with the adjacent lung are lacking. The pleural effusion is without apparent associated thickening, best assessed after the administration of intravenous contrast. Exudative effusions however frequently have loculations in addition to enhancement of the parietal pleura. A lack of parietal pleural enhancement on contrast-enhanced CT, however, does not exclude an exudative pleural effusion (Fig. 80) (572). Parietal pleural thickening was less frequently associated with malignant effusions than with parapneumonic effusions in a study assessing CT characteristics of pleural effusions (572). The presence of contents of higher attenuation than soft tissue density raises suspicion of pleural hemorrhage. Soft-tissue attenuation within the pleural space may represent malignant deposits or evolving hemorrhage. The presence of air in the pleural space raises question of a bronchopleural fistula in the scenario of an infection. Other etiologies for air include recent thoracentesis or pleural intervention, penetrating trauma, pneumothorax, and empyema with gas forming organisms. Minimal pleural fluid may be difficult to differentiate from dependent atelectasis or pleural thickening.

Difficulty may ensue when attempting to localize a large fluid collection to the pleural space as opposed to the lung. The differentiation of these two entities is often clinically significant, as a pleural effusion may be treated with catheter drainage whereas a lung abscess would not. The loculated pleural fluid collection frequently has an elliptical appearance in the axial section, forming obtuse angles with the adjacent chest wall and mediastinum (Fig. 81). However, loculated effusions may appear extremely round, form acute angles with the chest wall and mediastinal structures, and therefore mimic a lung parenchymal process such as a lung abscess. In these scenarios, the assessment of the overall shape of the abnormality in 3D is useful. Pleural collections, while they may appear round in the axial section, often are oblong in the cranial caudal dimension, whereas a lung abscess tends to be spherical. A lung abscess also replaces and destroys the lung parenchyma, and therefore blood vessels in the adjacent lung do not appear as displaced as with a pleural process. Additionally, the wall of a lung abscess tends to be irregular and thick while a pleural process tends to be smooth in contour. In the scenario of a loculated pleural collection, signs of pleural fluid elsewhere may be lacking and therefore are not always useful for differentiating pleural and lung processes. Also, a lung abscess and loculated pleural collection may coexist in the same location within a hemithorax, with the empyema related to rupture of the lung abscess into the pleural

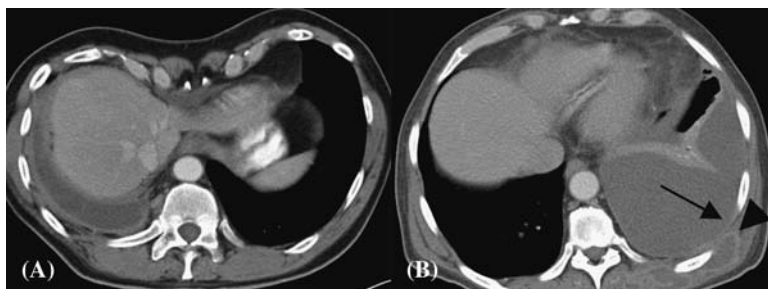


Figure 80 (A) Split pleura sign. Chronic pleural thickening and enhancement of the parietal pleura is demonstrated consistent with an exudative effusion in this patient with an empyema. The presence of pleural thickening or enhancement suggests the presence of an exudative effusion; however, the absence of this finding has a low specificity for the determination of a transudate. (B) Pleural enhancement and empyema necessitatis. A large effusion is demonstrated with areas of pleural tethering of the lung parenchyma and pleural enhancement (*arrow*) suggestive of an exudative process. The arrowhead demonstrates decompression of the empyema into the subcutaneous tissues with formation of an abscess. This appearance of empyema necessitatis is highly suggestive of infection most typically tuberculosis.

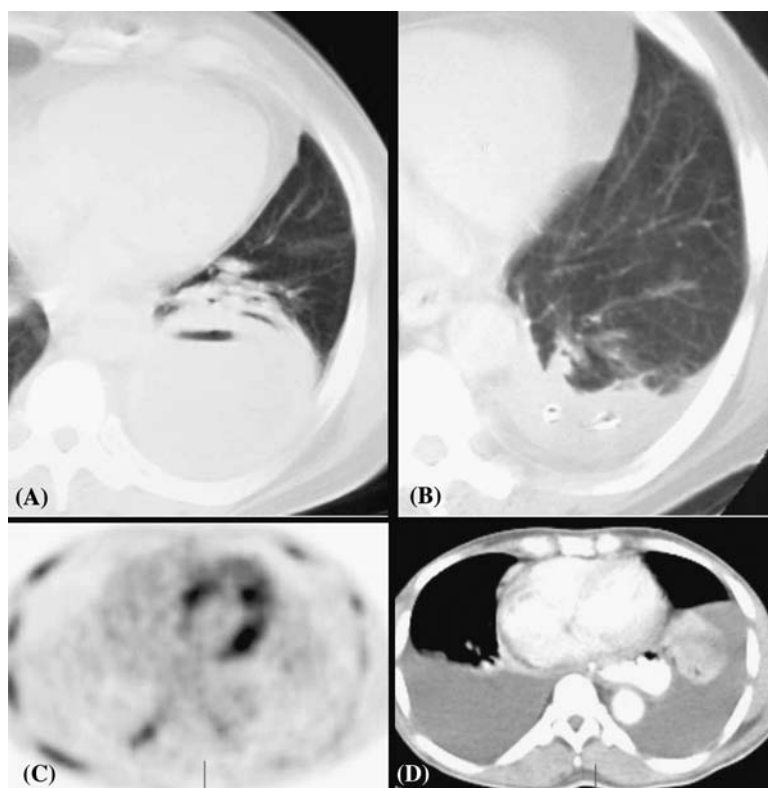


Figure 81 Loculated pleural fluid collections after (A) and prior to (B) catheter drainage. Loculated pleural fluid frequently has an elliptical appearance on axial sections, forming obtuse angles with the adjacent chest wall. However, acute angles may occur (B) thereby mimicking a lung abscess. Note the anterior displacement of the left lower lobe vessels and the smooth inner wall that are often seen with loculated pleural collections (B) and less commonly with lung abscesses. The air in the pleural collection in (B) was introduced during pleural sampling. Air can be introduced into a pleural collection when adjacent lung infection ruptures into the pleural surface, leading to an often-transient bronchopleural fistula. After drainage (A), the adjacent lung is reexpanded without destruction. In another patient with benign pleural effusions, PET (C) shows no uptake, corresponding with bilateral pleural effusions on CT in (D). The increased uptake in the periphery of the chest localizes to the ribs secondary to bone marrow stimulation in this patient who was being treated for neutropenia after chemotherapy.

space. An infected bulla may also be difficult to differentiate from a lung abscess or loculated pleural fluid collection.

Fluid may become loculated within a fissure leading to a finding that simulates a lung nodule. The loculated fluid, termed a “pseudotumor” given its similarity to a lung lesion, is characteristically aligned however along the fissural surfaces and is often elliptical in shape (rather than round) with often hazy borders. When confident measures of attenuation can be made, determination of fluid density is highly suggestive when accompanied by the other typical features.

Benign Pleural Thickening

Benign pleural thickening is typically associated with a chronic pleural effusion (573). Pleural thickening, as described above, when nodular and very thick, raises suspicion of a malignancy. Pleural thickening when diffuse, smooth, and long standing has been termed a fibrothorax and is typically associated with volume loss of the affected side. When calcified, the term calcified fibrothorax has been used and been associated with entities that include tuberculosis pleurisy (Fig. 82) empyema and hemothorax (573). Calcifications may involve both the visceral and parietal pleura. The visualization of prominent extrapleural fat peripheral to the pleural processes raises question of a chronic component of pleural thickening and effusion. The prominent extrapleural fat is felt to represent expansion of the fat in response to volume loss in the affected hemithorax.

Asbestos-Related Pleural Disease

Asbestos-related pleural disease secondary to asbestos exposure includes pleural effusions, pleural plaques, and diffuse pleural thickening. Pleural effusions tend to occur

relatively early in comparison with other manifestations of asbestos lung and pleural disease, typically 10 to 20 years after exposure to asbestos (574). Pleural plaques are frequently encountered later approximately 20 to 30 years after exposure, appearing as focal nodular ovoid densities in the periphery of the lung associated with the parietal pleura (574). The plaques tend to lie in the inferior aspect of the ribs occupying less than one interspace, affecting the diaphragmatic surfaces in addition to the posterolateral aspects of the thorax (Fig. 83). Interfissural plaques can be seen occasionally. The plaques can be noncalcified or calcified. The presence of bilateral calcified scattered discrete and nondiscrete densities is suggestive of asbestos pleural disease. Diffuse pleural thickening may result from greater pleural inflammation, and varying definitions and criteria for its appearance on CT have been devised (456,575,576). Pleural thickening in asbestos pleural disease is smooth and involves a significant portion of the thorax, more than 25% of the chest wall on a radiograph, and typically greater than 5 mm in thickness as defined by McLoud (575). The costophrenic angles may or may not be obliterated. Round atelectasis is a parenchymal lesion related to asbestos pleural disease and has been described in focal benign lung disease.

Localized (Solitary) Fibrous Tumor of the Pleura

Localized (solitary) fibrous tumor of the pleura is a typically benign neoplasm unrelated to asbestos exposure and potentially curable with surgical resection. These lesions arise more commonly from the visceral pleura including the fissural regions (577). Referred to previously using varying terms including localized mesothelioma, fibrous mesothelioma, and pleural fibroma, this lesion presents typically in an asymptomatic individual. Localized fibrous tumor of the pleura has been described to

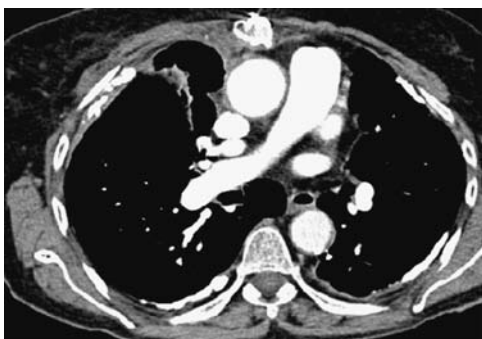


Figure 82 Fibrothorax. Bilateral coarse pleural thickening and pleural thickening is present secondary to remote mycobacterial infection. Although these findings are usually stable over many years, careful evaluation of the pleura is required in these cases to exclude new pleural thickening or extrapleural fluid, which may signify reactivation disease.

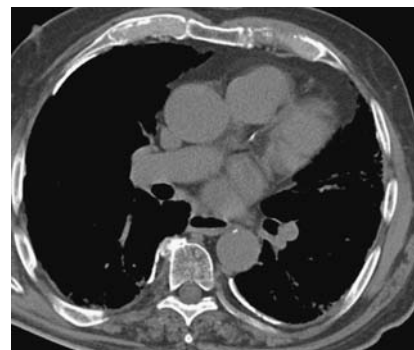


Figure 83 Asbestos-related pleural plaques—5-mm section. These are usually bilateral and may have or lack calcification. Although asbestos-related pleural disease may be isolated, in other cases it may coexist with other features of asbestos exposure including asbestosis, rounded atelectasis, mesothelioma, or lung cancer.



Figure 84 Benign fibrous tumor of the pleura. Patients with this large lesion may remain asymptomatic until a significant size. The heterogeneously enhancing lesion arises from the pleura and compresses the lung parenchyma (arrow). The lesion may be quite mobile and, despite the appearances of a relatively broad base, may be pedunculated. Therefore, on occasion appear to have acute margins to the pleural surface suggestive of a pulmonary lesion. Depending on the area biopsied, variability in the mitotic activity is the norm, and there may be areas with a more aggressive nature. Therefore, in most cases resection is advocated, even if the biopsy is benign.

cause hypertrophic pulmonary osteoarthropathy in which diffuse cortical thickening occurs typically in the extremities and leads to the formation of clubbing. Other symptoms that may be exhibited include hypoglycemia (577). These lesions vary in appearance, typically a well-defined lesion, often with lobulated borders, ranging from small to large in size (577). Lentiform or ovoid shape has been described while acute angles were more common in another assessment (577,578). Fissural tails were demonstrated in the lesions located in the fissures (578). The borders are well circumscribed with infrequent calcification and a lack of pleural effusions (Fig. 84). These lesions may shift in position during fluoroscopy or between imaging performed at different times, given their pedunculated nature and location within the pleural space. Contrast enhancement is common, leading to homogeneous or heterogeneous enhancement which is associated with larger tumors (577,578). Occasionally, these lesions may prove malignant with aggressive features of necrosis, cystic degeneration, and hemorrhage. Local recurrence can occur after resection.

SUMMARY

1. Mediastinal nodes greater than 1 cm short axis are considered pathological by CT.
2. Pseudonodes may be created by fluid-filled pericardial recesses, prominent cisterna cheli, and vascular variations that are difficult to identify on noncontrast CT. These lesions, however, will prove of low metabolic activity.

3. Multislice PET/CT units improve craniocaudal coverage and enable reconstruction of CT data into thin sections.
4. The thymus has variable size, with maximal size reached in the adolescence (and subsequent) gradual involution.
5. A nodule of low metabolic activity may still prove malignant such as with BAC, carcinoid, and malignancies of small size.
6. Popcorn calcification, fat, and low metabolic activity are indicative of a hamartoma.
7. PET/CT is particularly useful for management of the indeterminate nodule suspected to be benign and noninfectious including rounded atelectasis or a hamartoma. Also PET/CT provides useful additional information in patients with comorbidities and lesions not easily accessible to biopsy.
8. A pure ground-glass nodule may represent AAH (a premalignant form of adenocarcinoma), BAC, or inflammatory etiologies.
9. Soft tissue in a subsolid nodule correlates with an increased likelihood of having an invasive adenocarcinoma component and worse prognosis.
10. Lung carcinomas are difficult to categorize into different histologies by imaging. Adenocarcinomas however are the most prevalent and tend to be peripheral in nature. Central lesions that are accompanied by diffuse bulky adenopathy raise suspicion for small cell carcinoma.
11. Left paratracheal and aortopulmonary window lymph nodes lie medial to and lateral to, respectively, the ligamentum arteriosum. The left paratracheal lymph nodes are accessible by cervical mediastinoscopy, whereas the aortopulmonary lymph nodes are accessible only via an anterior approach.
12. PET/CT has higher sensitivity and specificity than CT alone in staging overall, although in restaging after induction therapy it has lower accuracy.
13. PET/CT is accurate in excluding mediastinal disease.
14. Invasive methods for staging the mediastinum include newer options such as endobronchial with a sound and endoesophage sampling techniques.
15. PET/CT has an accepted role in staging distant disease.
16. Evaluation of enlarged adrenal glands with CT (<10 HU) and PET ($SUV \leq$ liver or <3.1) improves specificity. Contrast enhanced adrenal CT can be used in more equivocal cases.
17. For bone metastases from non-small cell lung cancer, FDG PET may supplant bone scintigraphy because of increased specificity.
18. MRI rather than PET/CT should be used to detect brain metastases.

19. PET/CT is more accurate than CT for identifying liver metastases.
20. Accurate staging of non-small cell lung cancer is essential for optimal clinical management. Stage IIIB remains a heterogeneous group.
21. FDG PET is not currently a standard part of staging in small cell lung cancer, but it has been shown to improve staging of extrathoracic and distant disease.
22. Dynamic contrast-enhanced CT to assess blood flow and FDG uptake, as assessed by SUV, both have prognostic significance but may not always positively correlate.
23. PET/CT is incorporated increasingly into radiation treatment plans, but technical issues, including defining the metabolic boundary of tumor and dealing with respiratory motion, still remain.
24. CT criteria (RECIST guidelines) require a reduction of the largest tumor dimension by 30% to indicate a tumor response. PET may show a metabolic response sooner and more accurately in the setting of neoadjuvant therapy and at the end of therapy and therefore may offer a better indication of prognosis than CT.
25. An understanding of the normal post-lung resection findings is important in identifying tumor recurrence.
26. The initial symptoms of radiation pneumonitis develop 6 to 13 weeks after completion of therapy and will appear on CT one to three months after therapy. Fibrosis develops approximately 6 to 12 months after therapy. Postradiation change on PET/CT may persist for many months but should show stable or declining metabolic activity.
27. FDG PET and PET/CT can be very sensitive for recurrence when changes in morphology are subtle, e.g., in the hilum. PET/CT improves the specificity of recurrence detection over PET alone.
28. Lung metastases may present without a dominant nodule, as typically seen in a primary lung cancer.
29. FDG PET may demonstrate metabolic activity in benign parenchymal disease. The appearance of the lungs on CT may add specificity.
30. CT nodules due to infection or inflammation are difficult to differentiate from malignancy. The presence of air bronchograms in a poorly marginated pulmonary parenchymal density is more suggestive of pneumonia, although forms of BAC can have these characteristics.
31. Discrete nodules should raise the possibility of fungal or mycobacterial disease. Tree-in-bud and centrilobular nodules are more indicative of bronchiolitis.
32. Septic emboli may present as rounded or triangular-shaped nodules and may have a "feeding vessel."
33. Noninfectious inflammatory etiologies include Wegener's granulomatosis, other granulomatous vasculitides, rheumatoid lung disease, sarcoidosis, sarcoid-like syndromes, and amyloidosis.
34. Vascular related causes of nodules that can mimic neoplasm include pulmonary infarcts, hematomas, and contusions.
35. Diffuse parenchymal disease may accumulate FDG and can be better characterized using the CT images acquiring for attenuation correction, but optimal CT technique including high-resolution techniques may be required.
36. Micronodular disease on CT may be lymphohematogenous or centrilobular in distribution.
37. Diffuse reticular parenchymal lung disease without significant fibrosis may be caused by lymphangitic spread of tumor, edema, infection, and inflammatory entities.
38. When reticular opacities are accompanied by fibrosis, UIP, NSIP, and chronic hypersensitivity pneumonitis should be considered.
39. When there is ground-glass density or consolidation, infection is most likely. Careful review of the airways leading to an area of consolidation will help identify obstructing airway lesions that may represent tumor. FDG PET can sometimes help define the tumor versus the infection.
40. Decreased lung density is most commonly associated with emphysema and air trapping. Large and small airways disease results in air trapping.
41. Malignant pleural disease is most frequently metastatic.
42. Malignant pleural effusions are more likely associated with nodular soft tissue and irregular thickening in contrast to benign pleural effusions, but this is nonspecific.
43. FDG PET may be helpful in characterizing pleural involvement as benign or malignant.
44. MPM is related to asbestos exposure. CT may show a unilateral pleural effusion, nodular pleural thickening, interlobar fissure thickening, and tumor invasion of the chest wall, mediastinum, and diaphragm. FDG PET is expected to show metabolic activity, but its role is confined to equivocal cases and to staging of distant metastatic disease.
45. Benign pleural disease may be metabolically active, e.g., in the setting of talc pleurodesis.
46. When dealing with fluid collections in the chest, differentiation of loculated pleural effusions from fluid-filled lung abscesses is sometimes difficult. Displacement of the parenchymal vessels, an oblong shape, and a smooth contour of inner aspect of the collection wall are more suggestive of a pleural collection.

47. Bilateral calcified and noncalcified pleural plaques are suggestive of asbestos related pleural disease. Effusions, thickening, and rounded atelectasis are other asbestos related pleural disease manifestations.

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9

PET/CT in Breast Cancer

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BREAST CANCER

Breast cancer is a common cause of cancer deaths among middle-aged women. Prevention and screening have become important health issues in the common belief that detection of breast cancer at an early stage may have an impact on survival (1) or at least allows a less aggressive treatment (2). Whether or not clinical breast examination might reduce breast cancer morbidity and mortality through an early diagnosis is still a matter of debate (3). Several radiological tools have gained importance in the diagnostic algorithm of breast nodules. While mammography and breast magnetic resonance imaging (MRI) have a good sensitivity (4) in screening for breast cancer and in local recurrence detection, they both lack specificity, requiring histologic correlation of their findings. Spiral computed tomography (CT) can be employed in examination of breasts and axillary regions (5), but acquisition techniques should be very specific with optimized and focused scan protocols and injection techniques (6). Moreover, as Hounsfield unit values of benign and malignant lesions may overlap, other diagnostic methods are required.

Spiral CT and 2-[¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography (¹⁸F-FDG PET) are used for staging/restaging and follow-up in patients with breast

cancer. FDG PET has made inroads in monitoring patients after treatment, with an increasing role in differentiation between fibrosis and active tumor in the patient with abnormal anatomical findings on CT or MRI. Increasingly, FDG PET/CT is gaining importance in every aspect of the diagnostic workup of breast cancer, allowing high accuracy in the detection of local and recurrent disease in a “one-stop shop.”

SCREENING AND EARLY DETECTION

Conventional Imaging Procedures

Screening and early detection of breast cancers is better performed by means of mammography. A typical mammographic finding of breast cancer is an ill-defined opacity with stellate appearance and irregular borders, which infiltrates background tissue, causing distortions in adjacent breast architecture. Malignant calcifications are typically linear, small (<1 mm) in diameter, nonuniform in size, and clustered (7,8). Mammography is relatively quick to perform and inexpensive.

All these reasons make mammography the most useful tool for screening breast masses in women aged 50 to 69 years (9). However, its diagnostic value is strongly

affected by the expertise of the reader (10) and by the degree of compression of the mammary gland (6,11). Moreover, mammography shows low sensitivity in some instances such as (i) dense breasts, making it unsuitable for high-risk younger women (11,12), (ii) detection of ductal carcinoma in situ (DCIS) with faint or no associated calcifications, and (iii) multifocal cancer (11). Cancer detection rate can be increased by a double review of mammograms (13) and with the use of digital mammography, and its ability to perform tomograms, and computer-aided detection (14,15), with better resolution for DCIS (16).

Other supplemental methods such as breast ultrasound (US) and MRI are employed in selected patient populations in case of doubtful findings on mammography. US and MRI of the breast are also indicated in case of dense breast parenchyma with a palpable mass and negative mammography, in case of multifocal/multicentric cancer, in the evaluation of lesions found on only one mammographic view, or in case of positive axillary metastasis with negative mammography (4,11,17).

High-resolution breast US is usually employed in dense breasts and in differentiating between cystic and solid tumors revealed by mammography. Malignant solid lesions are usually irregular in shape on US with posterior shadowing (6).

The value of breast MRI in the diagnostic workup of breast cancer has been increasingly acknowledged because of its high sensitivity in detecting invasive ductal carcinomas. MRI, with the additional help of mammography, is now the best tool for the detection of DCIS, either isolated, or surrounding an invasive carcinoma, allowing the correct definition of tumor extent. False negatives have been documented in case of invasive lobular carcinomas, but this technique is still more sensitive when compared with other imaging modalities (4,6). The use of intravenous contrast during dynamic acquisition can add additional information (percentage of signal increase, continuous enhancement, plateau or washout) to increase tumor detection rate: malignant lesions usually display an early significant increase of signal. However, benign lesions, especially in young patients, can also be characterized by signal enhancement, as result of the physiological response to hormonal cycle. In order to lower the influence of hormonal variations on the pattern of enhancement, MRI is preferably performed in the second week of the menstrual cycle or, in the case of patients undergoing hormone replacement therapy, after two or three months from discontinuation of treatment (4). Despite the high lesion characterization that can be achieved using MRI, potential drawbacks limit its use in the widespread screening of breast cancer, mainly its high cost and the lack of standardization of the dynamic procedure (6). Moreover, because of its low specificity,

histological correlation is always necessary, and the use of MRI in guiding biopsies is still investigational (18). Therefore, applications of MRI for breast cancer screening are likely to be limited to women at high risk or with dense breast tissue (4,8,14,17).

Nuclear Medicine Procedures

Nuclear medicine procedures are not routinely employed in general screening for breast cancer, but a niche can be identified in cases where mammography has a lower sensitivity. In particular, scintimammography, either with technetium-99m methoxy-isobutyl-isonitrile (^{99m}Tc -sestaMIBI) or tetrofosmin, has shown good sensitivity and specificity in cases of dense breasts, for follow-up of patients previously having undergone surgery or radiation therapy for breast cancer, for contralateral monitoring, and when equivocal mammographic findings are present (19,20), i.e., the same situations in which breast MRI is indicated.

FDG PET and PET/CT

The radiotracer most widely used in clinical practice in the evaluation of breast cancer is the glucose analogue ^{18}F -FDG.

Several authors have investigated the accuracy of FDG PET in the detection of primary breast cancer (Fig. 1), with discordant conclusions (21–23). Overall, sensitivities and specificities ranged from 80% to 100% and 75% to 100%, respectively (24). To date, FDG PET is known to show low sensitivity in (1) lobular carcinomas, (2) more well-differentiated and slowly growing histologic subtypes (tubular and in situ) carcinomas, and (3) lesions smaller than 1 cm (24–26).

In fact, the sensitivity for detecting tumors less than 1 cm is 57% compared with 91% for tumors larger than 1 cm and can be as low as 25% for detecting carcinoma in situ (18). This difference is probably due to the degree of expression of biomarkers involved in cellular proliferation and metabolism within the tumor (Ki-67, glucose transporter-1, hexokinase, and hypoxia-inducible factor-1), which influence the amount of FDG taken up by tumor cells (27–29).

Attempts to improve FDG PET sensitivity have been made with prone (Fig. 2) (30,31) and dual-time-point acquisitions (30,32,33). A prone acquisition is performed in order to better discriminate between breast tissue and chest wall, as well as for a better comparison of PET and MRI (30).

Determination of dual-time-point standardized uptake values (SUVs) is made as an effort to discriminate between breast malignancies and inflammatory lesions. Kumar et al. (32) and Mavi et al. (34) demonstrated that

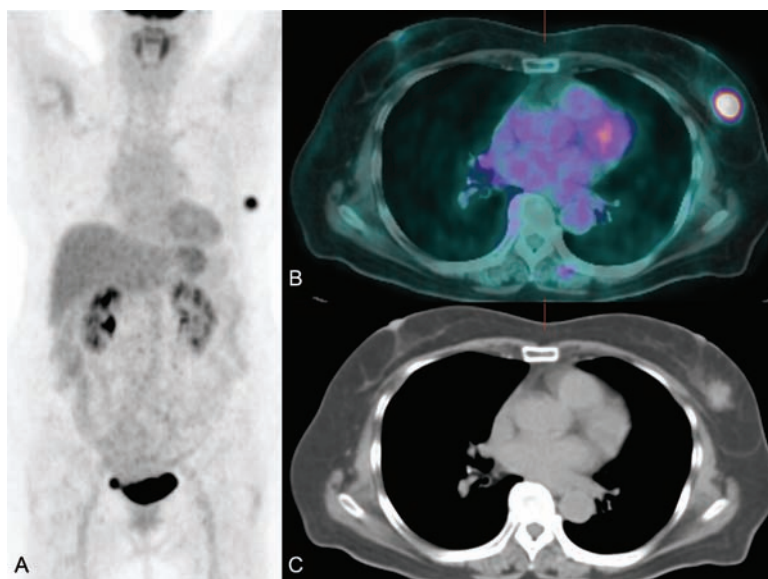


Figure 1 Primary carcinoma of the left breast without lymph nodal involvement or distant metastasis. (A) Maximal intensity projection (MIP) view shows a single prominent focus in the lateral left breast. (B) fused axial PET/CT view shows the intense uptake corresponding to the somewhat spiculated large soft tissue density on the (C) axial CT view.

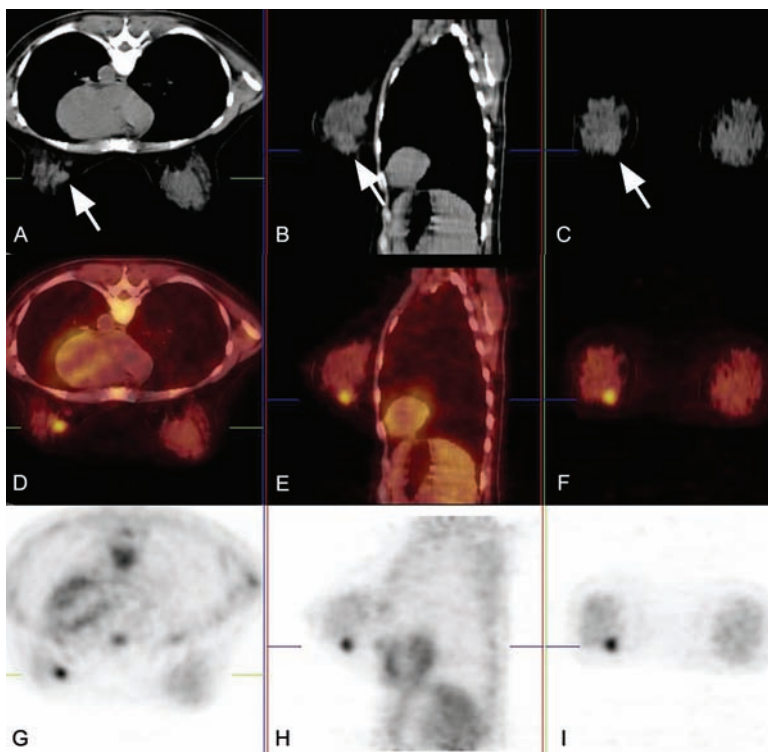


Figure 2 Prone imaging improves localization of breast lesion and increases the reader's confidence in characterizing a lesion as benign or malignant. Nodular lesion in the left lower inner quadrant seen on CT images (*arrows*) shows intense FDG uptake on fused FDG PET/CT images. On histology, this was found to be an invasive ductal carcinoma prone CT: (A) axial, (B) sagittal, (C) coronal; prone fused PET/CT: (D) axial, (E) sagittal, (F) coronal. Prone PET: (G) axial, (H) sagittal, (I) coronal.

FDG uptake increases over time in breast cancers, while SUV of inflammatory lesions and normal breast tissue remains stable or decreases. Mavi et al. (34) reported sensitivity for dual-time-point SUV of 90.1% and 82.7% for invasive cancers greater than 10 mm and 4 to 10 mm, respectively. Also, dual-time FDG PET showed a sensitivity of 76.9% in detection of noninvasive breast cancers. Because FDG uptake in malignancies is expected to increase over time, SUV in breast cancer was found to be more reliable at three hours postinjection of radio-tracer, leading to a better tumor/background contrast and reducing biological and interobserver variability (30). Mavi et al. (34) suggest that dual-time-point SUV, even measured with a mean time interval of 39 minutes between the first and the second scan, is more specific for detection of breast cancer. A more practical method to compare SUV acquired at different time points has been proposed (33), as the measurement of SUV at three hours postinjection is impractical in clinical setting.

PET/CT and MRI Fusion

As both MRI and PET/CT are frequently requested for disease evaluation for suspected breast cancer, a mechanism to foster direct comparison of lesions detected with both modalities would be useful to decrease the number of false-positive (FP) findings at MRI (35–37). The most significant limitation in comparing standard prone MRI images with supine PET images is the loss of normal landmarks. Some authors propose the acquisition of an additional limited PET scan of the chest in the prone position to increase the quality of the fusing process (35,36,38–41). In a study by Goerres et al. (36) comparing side-by-side prone ^{18}F -FDG PET and MRI studies, sensitivity, specificity, and accuracy were 79%, 94%, and 88%, respectively, for MRI compared with 100%, 72%, and 84%, respectively, for ^{18}F -FDG PET. However, position and shape changes in the breast between the MRI and PET occurred among all patients, especially in women with large breasts.

Since an in-line system that could allow functional PET and anatomical MRI images to be acquired in one session and rapidly co-registered is currently not available commercially, fusion of the metabolic information obtained by ^{18}F -FDG PET scans with the MRI scan can be improved, and the specificity of MRI can be increased using appropriate positioning devices, such as the one developed in our institution, designed to allow the patient to be imaged in a prone position, using a similar physical configuration to MRI during PET acquisition (42). To date, coregistration of MRI and PET images using semi-automated fusion software is still limited in clinical practice as it requires various steps (image transfer, reading, registration, and

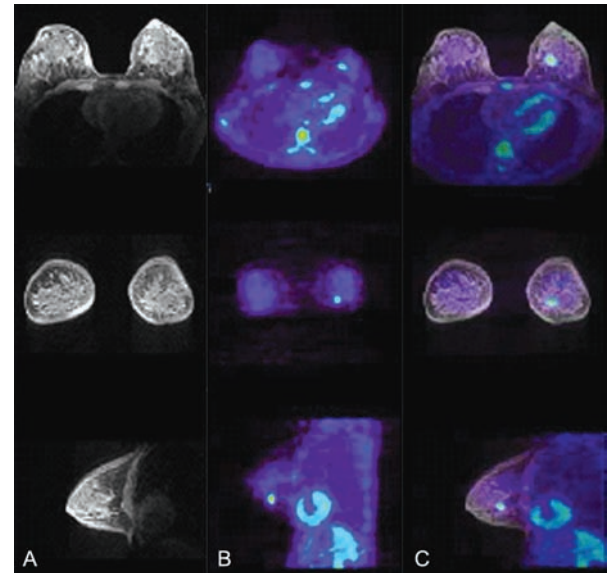


Figure 3 Example of coregistration of MRI and PET images in a patient with biopsy proven left breast carcinoma. A semi-automated fusion software can correct for differences in the patient positioning and increases MRI specificity, sparing the patient the trauma of more invasive procedures. (A) (Top to bottom) Prone axial, coronal and sagittal MRI. (B) Prone axial, coronal and sagittal FDG PET. (C) Prone axial, coronal, and sagittal coregistered PET and MRI images.

re-slicing) and is time consuming. However, it can correct for differences in the patient positioning and increase the reader's confidence in characterizing a lesion as benign or malignant. The increased specificity of MRI might then spare the patient the trauma of more invasive procedures (i.e., fine-needle aspiration, biopsy, or resection) or the anxiety and expense of a series of short-interval follow-up examinations (Fig. 3).

An interesting perspective is FDG-positron emission mammography (PEM), which integrates two planar detectors into a mammographic system, co-registering both mammographic and FDG images of the breast (43), with a spatial resolution of 2.8 mm (full width half maximum) (44). Rosen et al. (45) investigated the sensitivity of PEM in a pilot study, performed with low doses of FDG (74–93.5 MBq) and a five-minute acquisition time in breast lesions highly suspicious for cancer, with dimensions ranging between 0.8 and 6 cm. The reconstructed PEM images were compared with conventional mammography and histologic results. Sensitivity of PEM was limited on smaller lesions (range 0.8–1.5 cm), on posteriorly located lesions and at the site of fat necrosis, but costs were lowered. Berg et al. (46) have recently assessed its high diagnostic accuracy in 77 patients with breast lesions, including DCIS. Sensitivity was 86% in the first study and

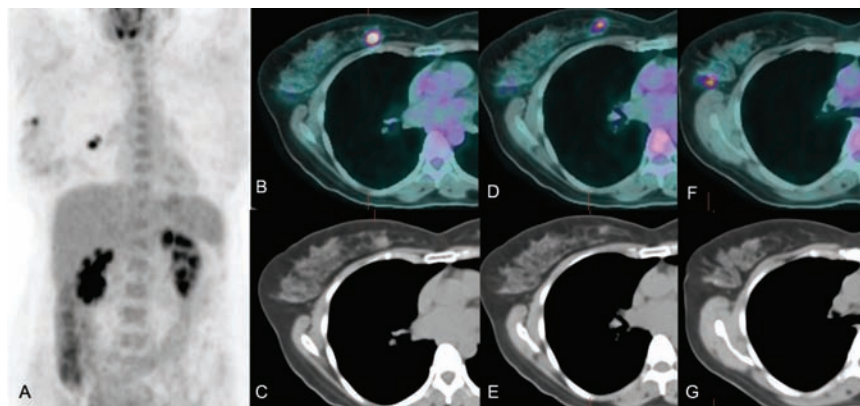


Figure 4 Additional value of PET/CT in the study of breast cancer. The new in-line PET/CT systems increase the specificity of FDG scan. The maximum intensity projection (A) shows the characterization of multiple right breast lesions, two separate medial lesions (B,C) and (D,E) are active on PET and fuse to soft tissue densities on CT in the inner upper quadrant. An additional focus of activity (F,G) localizes to the outer upper quadrant, which was found to be a lymph node at surgery. The precise anatomical localization provided by fused PET/CT permits the localization of even small subcentimeter lesions and the semiquantification of their activity.

91% in the second one, which is not very different from previously reported FDG PET sensitivities (24), but PEM, with the help of mammographic findings, could potentially detect smaller and less FDG-avid breast tumors, and possibly with lower cost than whole-body PET.

Even though the recent availability of in-line PET/CT scanners may have partially improved FDG PET sensitivity in lesion localization (Fig. 4), current data do not support the use of FDG PET in primary breast cancer detection or staging. Therefore, in the United States, the Centers for Medicare and Medicaid Services is yet to approve the reimbursement for FDG PET in the initial diagnosis of breast cancer and the staging of axillary lymph nodes. FDG PET accuracy is still not comparable with the standard practice of mammography supplemented by ultrasonography and histologic analysis of specimen obtained from image-directed stereotactic needle biopsy (47). Moreover, its cost as a screening tool is too high and even though minimal, the whole-body radiation exposure following FDG PET cannot be justified by the possible benefits of this technique in a low-risk population (25).

TUMOR STAGING

Although tumor grade, lymphatic or vascular invasion and tumor type are included among the prognostic factors, TNM staging, i.e., tumor size and axillary node status, remain the most important factors (7,48). As with primary tumors, smaller tumor deposits and some histologic types can escape FDG PET detection. Better results can be obtained with the use of breast MRI or mammography.

Several authors reported their experience with FDG PET in patients with breast cancer for staging/restaging

(21,23,36,49–59) and monitoring after treatment (60–67).

Literature addressing the additional value of PET/CT in the study of breast cancer is still sparse (25,37,68–70). PET/CT offers high-quality fused images of both function and anatomy at the same location of the body, allowing the demonstration of pathological FDG uptake in small structures that are “negative” based on the CT size criteria. It also permits the exclusion of FDG uptake in the area of inactive scar tissues (Fig. 5) and clarifies the location of physiological FDG uptake, which might otherwise be misinterpreted as malignant on PET scan. In a study by Tatsumi et al., PET/CT was found to yield improved diagnostic confidence in 60% of the patients with increased FDG uptake. The frequency of improved diagnostic confidence ranged from 33% to 100%, with the exception of the liver (61).

Lymph Node Staging

The presence of lymph node metastases is the most important prognostic factor in breast cancer, along with primary tumor size. There is a proven positive impact on survival in case of early treatment of lymphatic dissemination (48). Sensitivities of FDG PET in nodal involvement range between 61% and 96% on axillary nodal tumor localization (Fig. 6) (23,49,50,52,71).

Avril (71) reported low sensitivities on axillary stations in stage pT1 patients, concluding that FDG PET is accurate in staging axillary nodes in patients with breast cancer with stage greater than T1. On the other hand, Gil-Rendo (50) reported a sensitivity of 100% in a subgroup of 50 women with stage III breast cancer. The above data

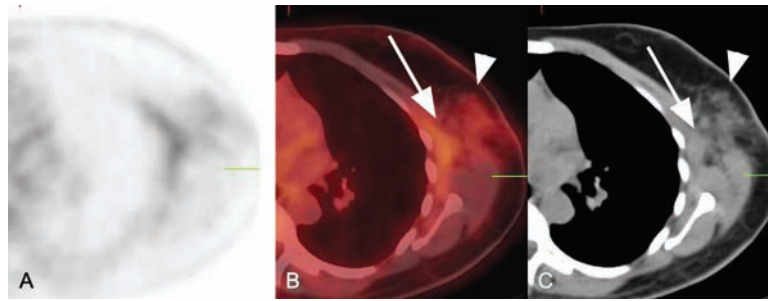


Figure 5 Example of utility of FDG PET in excluding recurrent disease in an area of prior treatment. The PET (A) shows just minimal FDG uptake fusing (B) to edematous changes (*arrowhead*) and newly forming scar tissue (*arrow*) in the left axilla on the CT (C). This resolved on follow-up study without interval therapy.

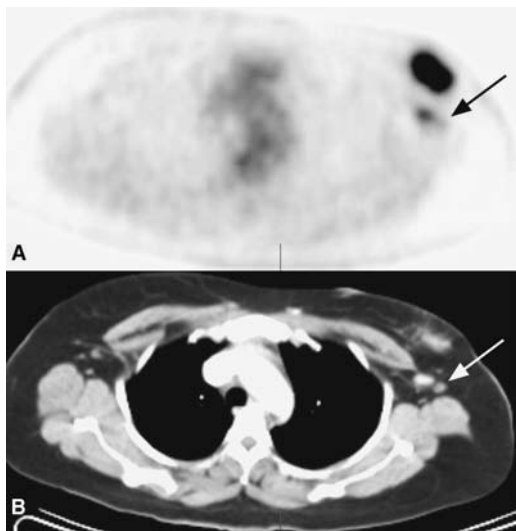


Figure 6 Localization of abnormal FDG uptake in axillary nodes in patient with primary left breast cancer. This illustrates the limitation of PET (A) in assessing the involvement of a small axillary lymph node (*arrow*). Although there is clearly an active lymph node in the left axilla, the second smaller more lateral lymph node (*arrow*) seen on CT (B) cannot be fully evaluated because of limited spatial resolution.

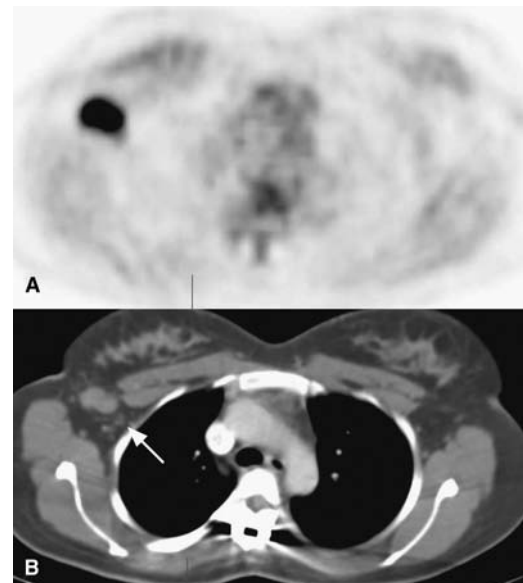


Figure 7 Localization of abnormal FDG uptake in axillary nodes in patient with primary right breast cancer. Limitation of PET (A) in assessing the number of involved axillary lymph nodes. The blurring effect of the intense activity in the enlarged right axillary nodes does not allow full evaluation of small adjacent nodes (*arrow*) seen on CT (B).

confirm the limitation of PET's ability to detect small-volume axillary disease in early-stage breast cancer (Fig. 7). Therefore, FDG PET cannot be used to replace axillary node sampling for routine staging of the axilla. Given its inherent limited spatial resolution, FDG PET cannot assess the presence and the characteristics (e.g., extranodal extension) of the lymph nodal involvement, both of which affect prognosis and treatment planning (72,73).

Reporting a study comparing FDG PET and sentinel lymph node (SLN) biopsy in patients with T1N0 breast cancer, Crippa et al. (52) found a significant difference

between the two methods in case of limited axillary involvement and similar sensitivity in detecting lesions greater than 5 mm, supporting the use of limited resolution of PET scanners. In similar surveys, Zornoza (51) and Gil-Rendo (50) suggest the use of SLN in case of FDG PET negative scans, but not when axillary foci of FDG uptake are seen. PET has the highest diagnostic performance on axillary staging with more advanced primary breast cancers greater than 2 cm, as nodal involvement is less frequent in lower stages (57). These data seem to agree with the present guidelines for the locoregional treatment of invasive breast cancer (48), which do indicate

lymph node mapping in cases of invasive breast cancer greater than 2 mm or tubular cancer greater than 10 mm.

FDG PET may be complementary to SLN mapping in patients with high risk of nodal metastases and palpable axillary nodes. In these cases, SLN mapping may give FP results because lymph flow is diverted around a node “packed” with a large volume of disease (74). Given its high positive predictive value (PPV), FDG PET may identify patients with evidence of nodal metastases indicating the need for standard axillary nodal dissection, rather than SLN biopsy.

Only few authors reported about FDG PET performance on internal mammary (Fig. 8) and mediastinal lymph nodes, alternatively comparing PET with CT (54), chest X ray and CT (53) or SLN (51). All these papers tend to suggest the superiority of diagnostic performance of FDG PET in detection of internal mammary/mediastinal spread, although histologic confirmation is not always the standard of reference. In fact, internal mammary lymph (IML) node involvement is quite rare (2–9%) (75) and their sampling has been questioned, even after a FDG PET diagnosis (52), because they are not easily accessible and their treatment with radiotherapy failed to yield improvements in survival (76).

However, some authors have shown that the prevalence of IML FDG uptake in patients with locally advanced breast cancer (LABC) can be as high as 25% and that the presence of IML FDG uptake predicts treatment failure (53).

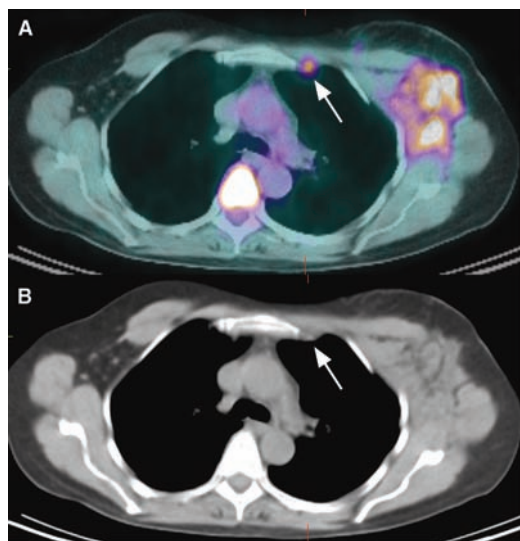


Figure 8 PET/CT shows an unexpected internal mammary lymph node involved from a lateral breast cancer. The new in-line PET/CT systems increase the specificity of FDG scan in small structures. The fused PET/CT (A) illustrates multiple active left axillary lymph nodes seen clearly on CT (B) and the intense FDG uptake corresponding to a small, more subtle lymph node in the left internal mammary chain (arrow).

Additional diagnostic value in lymph node staging and thorax evaluation, mainly due to better lesion localization has been improved with in-line PET/CT (37). In fact, the exact anatomical mapping of an FDG-avid focus in the chest and its exact meaning is often difficult with PET alone, and may result in over/under staging of disease.

DETECTION OF RECURRENT DISEASE

Local Recurrence

After breast surgery, half of patients relapse locally, most commonly in the chest wall and in the supraclavicular region, while the other half have distant metastatic lesions at the time of recurrence. FDG PET has shown some value in the evaluation of local recurrence, with the advantages of a whole-body examination in a single imaging session and the possibility of discriminating between active disease and posttreatment scar tissue (Fig. 9) in cases of breast-conserving surgery or irradiated breasts.

Another advantage of FDG PET is its good sensitivity in residual tissue in the setting of breast implants (Fig. 10). Performance of FDG PET in local relapse has been compared with MRI (36,59) and with conventional imaging (CI) (57,58). In the first study (59), 9 of 10 patients were positive on FDG PET and 5 of 10 on MRI. In the second, Goerres et al. (36) compared FDG PET and MRI performance in 32 patients with suspicious loco-regional recurrence, chest wall recurrence, or suspicion of secondary tumor on the contralateral side. Sensitivity, specificity, and accuracy were 100%, 72%, and 84% for FDG PET and 79%, 94%, and 88% for MRI. Moreover, PET detected metastases outside the field of view of MRI in five patients (15%). Wolfort et al. (58) reviewed the results of FDG PET and conventional imaging (CI), histological findings and clinical follow-up in 26 breast cancer patients with a history of stage II–III disease and a

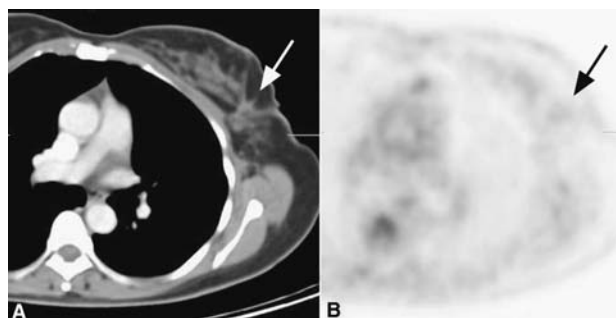


Figure 9 FDG PET/CT is particularly useful evaluating areas of scar tissue seen (A) on CT(A). The corresponding axial PET image (B) shows no abnormal FDG uptake corresponding to scar tissue (arrows) in the left breast in the region of prior lumpectomy.

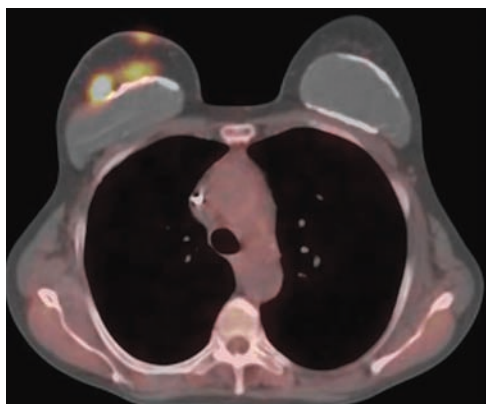


Figure 10 PET/CT is also helpful in the evaluation of recurrent disease in patients with breast implants. This prone PET/CT image shows intense metabolic activity fusing to new lesions felt superficially to the right breast implant on physical examination, highly suggestive of local recurrent disease. The PET/CT findings were confirmed at biopsy.

suspected local recurrence. FDG PET sensitivity was 75% on stage II patients, 83% on stage III patients, and 81% overall. Gallowitsch (57) did not find significant differences between FDG PET and CI in the detection of local recurrences in a lesion-based analysis.

Assessment of Extent of Distant Metastatic Disease

When disease recurrence is suspected, imaging studies become necessary to stage the extent of disease since oligometastatic disease or small volume metastases may benefit from combined multimodality treatment, while metastatic breast cancer is treated with palliative intent (7).

The value of FDG PET in the assessment of distant disease has been studied by several authors (56–58,77). In a series of 57 patients, Moon et al. (77) reported that positive predictive values and negative predictive values were 82% and 92%, respectively, for FDG PET scans in patients who presented with clinical suspicion of recurrence. Gallowitsch (57) showed that PET performed better than CI on per-patient analysis (sensitivity 97.1% and 84.8%, respectively), and that it detected more lymph nodes and fewer bone lesions than CI on per-lesion analysis. Kamel et al. (56) reported an FDG PET sensitivity of 100%, specificity of 97%, and an accuracy of 98% in a patient-based analysis in a population of 60 breast cancer patients with clinical or radiological suspicion of recurrence. Wolfort et al. (58) investigated 23 patients with stage II–III disease presenting with suspicion of recurrence and found that the sensitivity, specificity, and accuracy were 81%, 100%, and 87%, respectively.

Again, reported experience with FDG in-line PET/CT is sparse (37,68,69), but data published confirm a better accuracy of PET/CT over PET alone.

FDG PET and Tumor Markers

Monitoring of tumor markers, either circulating or tissue based, can be useful at different stages of breast cancer, but are commonly used to detect treatment failure (78,79). A few authors have evaluated FDG PET performance in the clinical setting of elevated serum tumor markers, in order to assess the diagnostic value of PET in the setting of “biochemical” recurrence (Table 1), concluding that the combination of FDG PET and elevated tumor markers suffice for an early detection of recurrence. Gallowitsch et al. (57) found that sensitivity and specificity of FDG PET in detecting recurrent disease were higher than conventional imaging in patients with normal tumor markers; the advantage of PET was somewhat less in patients with tumor marker elevation. In fact, 11 of 31 patients with negative markers had clear evidence of recurrent disease, most commonly limited (three local recurrence, four mediastinal lymph nodes, four bone metastases). In the same study, conventional imaging methods showed lower diagnostic accuracy, and since they show low sensitivity with low tumor burdens such as occurs with negative serum tumor markers, recurrence of disease could not be excluded. On the other hand, FDG PET can also be false negative in case of relapse (80) even with elevated tumor markers, because of limited spatial resolution and lack of anatomical mapping. The wider availability of PET/CT scanners, in this clinical scenario, may allow earlier and more accurate diagnosis of recurrence.

Bone-Dominant Disease

The role of FDG PET in the evaluation of bone metastases in metastatic breast cancer is still a matter of debate. Factors that can influence FDG or other radiotracers uptake within bone metastases are extensively discussed in a dedicated chapter in this book.

Breast cancer often metastasizes to bone, and no consensus still exists about which one is the most sensitive method of detecting and determining the extent of skeletal metastases.

Skeletal scintigraphy, with the added value of SPECT acquisition, plain radiography, CT, and MRI have all made venues (81). FDG and sodium-fluoride PET, and more recently PET/CT, have demonstrated diagnostic value (82–84). Also, the ability to perform a whole-body CT in a single imaging session of PET/CT allows diagnosis of sclerotic bone lesions that might be missed by PET alone (83) and a timely detection of cord or nerve impingement.

Table 1 Performance of FDG PET in Case of Elevated Circulating Tumor Markers

Author (reference)	Year	Number of patients	Tumor marker	Sensitivity (%)	Specificity (%)
Lonneux (112)	2000	39	CA 15.3 $\pm$ CEA $\pm$ CA 549	94	50.5
Pecking (113)	2001	132	CA 15.3	93.6	96.2
Suarez (114)	2002	45	CA 15.3 $\pm$ CEA	92	75
Liu (115)	2002	30	CA 15.3 $\pm$ CEA	96	90
Siggelkow (116)	2003	57	CA 15.3	80.6	97.6
Kamel (56)	2003	25	CA 15.3	100	97

The ability to quantify and monitor over time any ongoing treatment is still investigational (85), even though Stafford et al. (86) have reported some value of SUV measurement in a small cohort of patients.

An extensive review of the literature on FDG PET in bone metastases from breast cancer is given in Table 2 of chapter 13, "Detecting and Evaluating Osseous Metastases on PET/CT."

MONITORING RESPONSE TO TREATMENT

LABC is defined as a primary tumor larger than 5 cm, presenting with clinical signs of mastitis carcinomatosa, skin, or chest wall involvement or disease spread to axillary, ipsilateral internal mammary, or supraclavicular lymph nodes. It has a poor prognosis that depends mainly on the response to neoadjuvant chemotherapy and on the presence of distant secondary localizations (7,48).

Early assessment of response to preoperative therapy has a strong predictive value for selection of patients for further chemotherapy and to improve tumor resectability (7,64). Conventional methods of assessing response to therapy, such as physical examination, mammography, or US, depend on anatomic characteristics of tumors and are often limited or slow to detect interval changes of the malignant characteristics of breast masses (87).

Potentially, MRI could monitor response to therapy in women with LABC or large tumors (88), but its sensitivity may decrease during chemotherapy (14,22). FDG PET has been proven to have value in monitoring early response to neo-adjuvant treatment in LABC both alone (61) or in combination with MRI (62), allowing also the definition of distant disease (8% in one series of LABC patients) (55). Other authors have reported FDG PET performance in monitoring treatment response (Table 2).

PET seems to have a major role in assessing fibrotic disease versus viable tumor in an early posttreatment setting, when conventional imaging (CT or MRI) still shows abnormality (Fig. 11). In fact, since shrinkage of tumor is not an early phenomenon after chemotherapy initiation, conventional imaging cannot accurately select responders versus nonresponders at an early stage. FDG

cellular uptake reflects the metabolic status of the tumor and, thus, can predict response to therapy earlier in the course of treatment (60,89).

Nonetheless, the best method and timing to quantify FDG uptake during follow-up is still an issue, and seems to be less effective for tumors displaying low contrast on pretherapy PET scans (63). "Flare," i.e., apparent tumor progression and "stunning," i.e., low radiotracer uptake after initiation of treatment, phenomena have been described and quantified by PET (90–92), but the timing and consistency of their occurrence is not well documented.

For example, Mortimer and coworkers reported a series of 40 patients with estrogen receptor (ER) positive breast cancer who underwent FDG PET for the evaluation of response to antiestrogen therapy (93). A "metabolic flare" of FDG uptake 7 to 10 days after institution of therapy predicted a subsequent response to therapy. Another novel application is dynamic PET imaging with ^{15}O -water, which can estimate regional blood flow within a tumor. The evaluation of pretherapy FDG uptake along with tumor perfusion rate has been demonstrated to predict complete pathologic response and disease-free survival in patients with LABC (94).

Future Development

A possible use of FDG PET/CT, with or without the help of MRI, may be useful for radiation therapy planning. Discrimination between viable tumor versus surrounding necrosis can be helpful in correct delineation of gross tumor volume, an approach currently used in radiation planning for lung and head and neck tumors. PET imaging appears to be particularly suitable for evaluation of expression of biomarkers specific for breast cancer especially for more advanced disease, where target expression can be heterogeneous. A variety of targets are under investigation, including ER (tamoxifen and letrozole), HER2 [trastuzumab (Herceptin)], EGFR [gefitinib (Iressa)], and angiogenesis factors [bevacizumab (Avastin)] (95).

Several studies have already been conducted evaluating the role of PET imaging in measuring expression of receptors such as ER (94,96,97) and HER2 (98), in

Table 2 Sensitivity and Specificity of FDG PET in Defining Treatment Response in Patients with Breast Cancer

Author (reference)	Year	Number of Patients	Sensitivity (%)	Specificity (%)
Smith (66)	2000	30	90	74
Schelling (64)	2000	22	100	85
Vranjesevic (65)	2002	61	93	79
Eubank (67)	2004	125	94	91
Santiago (117)	2006	133	69	80

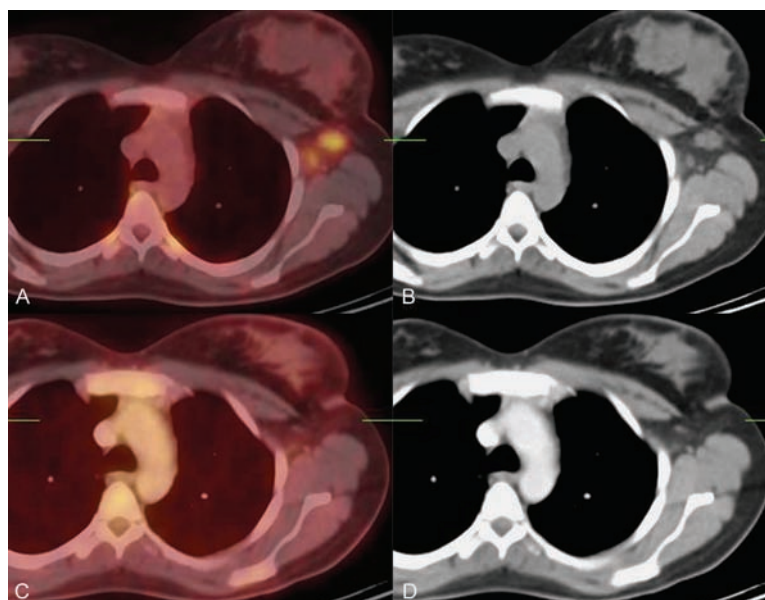


Figure 11 Monitoring response to therapy. Pretherapy fused PET/CT scan (A) shows activity in two left axillary lymph nodes seen on CT (B) compatible with metastatic disease. Of note, there is also evidence of increased FDG uptake in the posterior intercostal region bilaterally related to brown fat activation. Posttherapy fused PET/CT scan (C) shows interval resolution of activity in the left axillary lymph nodes which appear smaller on CT (D) compared with the prior scan.

quantifying angiogenesis, (94,99–102) and measuring novel targets such as matrix metalloproteins (103) and vasoactive intestinal peptide (93).

An analog of estradiol, the labeled estrogen, 16-[F-18]-fluoroestradiol-17 (FES) (104) has been shown recently to be suitable in quantifying the functional ER status of breast cancer and to predict response to hormonal therapy. Another promising application of PET imaging relates to the study of expression of resistant factors to therapy such as HER2 (105), P-glycoprotein (P-gp) (106), altered DNA repair mechanisms (107), and tumor hypoxia (108,109). ^{18}F -fluoromisonidazole is the tracer that has been more widely used in the study of tumor hypoxia (110,111).

SUMMARY

FDG PET and PET/CT may have a role in detection of breast cancers, but in a very limited and specific setting. FDG PET has shown moderately high sensitivity for

detecting primary tumors, but is less effective in lobular carcinomas, slowly growing tumors, and small tumors. Using prone PET acquisitions, dual-time-point imaging and registering FDG PET with MRI has increased the sensitivity and specificity of PET for primary breast cancer. Dedicated FDG PEM may also improve on sensitivity.

In tumor staging, tumor size and axillary lymph node status are the most important prognostic factors and determinants of further clinical management. Although PET lacks sensitivity for micrometastasis and is unlikely to replace sentinel lymph node biopsy, the use of FDG PET to detect and establish the presence of macro-disease, may help with direct progression to axillary node dissection rather than biopsy. FDG PET may also help establish the presence of IML node disease in locally advanced breast cancer. In monitoring for recurrence, FDG PET and PET/CT may be helpful in differentiating between scar and recurrent tumor and will more quickly establish the presence of distant disease.

Furthermore, FDG PET has had utility in patients with implants post reconstruction.

In assessing the presence of distant disease, PET and PET/CT have shown improved sensitivity for assessing tumor burden, especially in the setting of elevated tumor markers. However, when tumor markers are low, FDG PET may offer even greater advantages over conventional imaging. In bone-dominant disease, FDG PET has a slightly less clear-cut role. The value of FDG PET in bone-dominant disease has increased with in-line PET/CT. Furthermore, PET may be useful in monitoring the response of bone metastases to therapy.

FDG PET and PET/CT offer improved sensitivity for response to neoadjuvant therapy in the setting of LABC over conventional modalities and can be used to direct further management. PET is also useful in differentiating fibrosis from residual viable tumor. New biomarker-specific radiotracers may advance the use of PET and PET/CT in determining therapy. Also, PET/CT may someday play a consistent role in radiation treatment planning for breast cancer.

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10

PET/CT for the Evaluation of Diseases of Gastrointestinal Origin

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INTRODUCTION

Positron emission tomography/computed tomography (PET/CT) has been used effectively in the evaluation of esophageal and large-bowel primary tumors. Its role in gastric and small-bowel tumors is less well acknowledged, although in lymphomas of the gastrointestinal (GI) tract and gastrointestinal stromal tumors (GISTs), fluorodeoxyglucose (FDG) PET/CT has played an important role in staging and evaluation of treatment response. In primary tumors of the liver, PET/CT has a less clear cut role because of decreased sensitivity in well-differentiated tumors, but in metastatic disease, FDG PET has shown advantages over even magnetic resonance imaging (MRI) (1). In pancreatic cancers and cholangiocarcinomas, non-mucinous tumors tend to be more FDG avid; the islet cell tumors of the pancreas and mucinous adenocarcinomas are less so. Sensitivities of PET for both primary tumors and metastatic tumors of these origins may be insufficient for staging or following therapy (2). The role of FDG PET/CT in staging and following patients will depend primarily on the

FDG avidity of the tumor versus the need to use a very tailored contrast-enhanced CT to evaluate these cancers. In addition there is a well recognized occurrence of incidental findings in the gastrointestinal tract on FDG PET, generally in 1% to 3% of patients examined for other cancers, that can be better elucidated with the addition of the registered CT, and that will have clinical significance (3,4).

Technical Aspects

In order to optimize CT imaging of the bowel, oral contrasts are essential. The bowel wall cannot be adequately assessed if collapsed and may even lead to misinterpretation and overestimation of disease. An intravenous (IV) or intramuscular injection of an antiperistaltic agent can improve image quality although it may interfere with interpretation of PET/CT. Barium paste, or a combination of water or neutral oral contrast with effervescent powder, can help achieve distention of the esophagus and stomach and improve visualization of the mucosa. Neutral or low attenuation oral contrast agents used in combination with IV

contrast can help distend the stomach and small bowel (5), but if no IV contrast is administered a positive or high attenuation contrast agent such as barium or gastrograffin is preferable. As always, dilute barium is preferable since dense barium can lead to changes in measured standardized uptake value (SUV) (6). Less clear is whether barium itself may act as an irritant or stimulus causing a physiologic increase in FDG uptake (6). For colonic imaging, oral contrast may not permit sufficient distention, rectal high attenuation contrast or rectal air may be warranted to optimize visualization of the colonic mucosa. 3D reconstructions and volume rendering are invaluable postprocessing tools for assessing bowel pathology. These protocols differ significantly from diagnostic CT protocols where timing of contrast, both IV and oral, can be more tightly controlled because only one part of the body, or even a particular organ, is being imaged (Table 1).

ESOPHAGUS

PET/CT is useful in the evaluation of esophageal malignancy and has applications in TNM staging. Normal variants on FDG PET must be considered and some attention to CT technique is helpful even in the context of PET/CT.

Normal and Benign Diseases

The esophagus extends from the level of the cricopharyngeus muscle at approximately C5–C6 to the gastroesophageal junction (GEJ). Normal esophageal mucosa is smooth, thin (<3 mm), and featureless. On CT imaging, the esophagus is a tubular structure surrounded by fat in the posterior mediastinum and may normally contain air or contrast. Fluid or debris may indicate reflux or obstruction. Normal physiologic distribution of FDG in the esophagus is minimal and usually less than the level of activity in the mediastinum or liver and without significant focal areas of uptake. Variants are primarily related to esophageal resection and subsequent altered motility and musculature, or to inflammation.

Familiarity with non-cancer-related surgical procedures such as fundoplication performed for severe gastroesophageal reflux is important. A portion of the stomach is wrapped around the GEJ and can mimic an esophageal neoplasm (Fig. 1). Obese patients may undergo a laparoscopic gastric banding procedure with a radiopaque band placed around the proximal stomach to restrict food intake (Fig. 1). This device is connected to a saline infusion port placed in the subcutaneous tissues, which is used to modify the tightness of the band.

Focal

A common incidental finding on CT imaging is a sliding hiatal hernia. By far, the most common esophageal hernia

is the sliding hiatal hernia (Fig. 2). Less commonly, hernias may be paraesophageal. Occasionally, the entire stomach can be intrathoracic with varying degrees of rotation, which can lead to abnormal twisting and obstruction, i.e., volvulus. Hiatal hernias may also demonstrate increased FDG activity, but are distinguishable from the more significant pathology by using the concomitant CT images (7,8). Diverticula are seen typically in the lower third of the esophagus. These eccentric outpouchings are usually related to esophageal dysmotility and can be filled with air and debris.

Congenital abnormalities of the esophagus are rare and include esophageal duplication cysts. They are most commonly located in the distal esophagus and do not communicate with the lumen (Fig. 3). They may contain ectopic gastric or pancreatic mucosa. These also have not been described on FDG PET. Duplication cysts typically present on CT as simple unilocular fluid density cysts with a thin wall, but may be complicated by hemorrhage, proteinaceous debris, and infection. Infection can lead to wall thickening, enhancement, and air-fluid levels. Duplication cysts can also occur in the small bowel, stomach, and colon.

It is important to note that ascites fluid may extend through the diaphragmatic hiatus and mimic a cystic lesion abutting the esophagus. So, in the setting of abdominal ascites, focal periesophageal ascites should be considered.

Benign tumors are rare, but are most commonly mesenchymal tumors, including leiomyomas, fibrovascular polyps, hemangiomas, and neurogenic tumors such as schwannomas and neurofibromas. Leiomyomas are the most common type and present as well circumscribed masses arising in the muscular wall of the esophagus or in the submucosa, and are most often located in the distal esophagus. Fibrovascular polyps are variable in density as they can be composed of varying amounts of fat and fibrovascular tissue. These fibrovascular polyps more typically arise in the upper esophagus, but can grow, elongate, and extend into the distal esophagus. Other submucosal lesions such as squamous papillomas are unlikely to be seen at CT. While leiomyomas (9) and neurofibromas (10) in other anatomic sites have been described as variably FDG avid, this has not been described in relation to the esophagus. Increase in FDG avidity has been associated with malignant transformation of neurofibromas (11). Schwannomas are usually FDG avid, but have not been described on PET in relation to the esophagus (12).

Hematomas can be seen secondary to trauma, interventional procedures, or anticoagulation therapy. Hematomas are usually well circumscribed, nonenhancing, intramural masses. In the acute stage, they will be hyperdense on noncontrast imaging, but become more fluid dense over

Table 1 Selected Diagnostic CT Protocols

Protocol	Phases of imaging	KV/mAs/ rotation	Slice thickness (recon)	Oral contrast	IV contrast rate; dose
Oncology survey ^a	Venous (90 sec) diaphragm to symphysis (thick) None	120/180/0.42		Dilute barium (1 L)	3 mL/sec; 1.5 mL/kg followed by 20 mL saline flush
Lower abdominal pain ^b	Venous (90 sec) diaphragm to symphysis (thin) None	120/180/0.42		Dilute gastrograffin 1 L (unless allergy)	3 mL/sec; 1.5 mL/kg followed by 20 mL saline flush
3 phase liver	NCCT ; liver (thick); arterial (bolus track/ add 15 sec)-abdomen (thin); venous (90 sec) diaphragm to symphysis (thin)	120/180/0.42	4 mm trans; 3 mm cor for contrast phases	500 mL water	5 mL/sec; 150 mL
Pancreas/ biliary/ stomach/ upper abdominal pain	Pancreatic phase (40 sec)- abdomen Only (thin); venous (90 sec) diaphragm to symphysis (thin)	120/180/0.42	4 mm trans; 3 mm cor	2 bottles negative contrast over 30 min (last cup immediately prior to scan) OR 1000 mL water	4 mL/sec; 1.5 mL/kg with 20 mL saline flush
Mesenteric ischemia	CTA phase (bolus track aorta) diaphragm to symphysis (thin); venous (90 sec) diaphragm to symphysis (thin)	120/180/0.42		2 bottles negative oral contrast over 30–45 min or 500 mL water	4 mL/sec; 1.5 mL/kg with 20 mL saline flush
CT colonography	Supine diaphragm to symphysis (thin); prone diaphragm to symphysis (thick)	120 kVP, 50 mAs ^b , 0.427–0.5 sec	4 mm	Rectal CO ₂	None
CT enterography	CTE phase (60 sec) diaphragm to symphysis (thin)	120/180/0.5		3 bottles negative oral contrast or 1000 cc water	4 mL/sec; 1.5 mL/kg with 20 mL saline flush
R/O AAA or dissection	NCCT of abdomen (thick); CT angiography; diaphragm-pubic symphysis (thin), track bolus to 150 HU	120/180/0.42	4 mm trans; 3 mm cor (phase 2)	500 mL water	5 mL/sec; 1.5 mL/kg (100 mL minimum) with 20 mL saline flush
Known AAA	CT angiography- diaphragm-pubic symphysis (thin)	120/180/0.42	4 mm trans; 3 mm cor	500 mL water	5 mL/sec; 1.5 mL/kg (100 mL minimum) with 20 mL saline flush

Thin indicates 0.75 mm (16 slice); 0.6 mm (40 or 64 slice) and thick indicates 1.2 mm (16 slice); 1.2 mm (40 or 64 slice).

^aFor breast cancer, carcinoid, islet cell, add noncontrast liver and first time lung cancer add NC through liver and adrenals with the same parameters.

^bScan 1 hr after administration of oral contrast; check cecum for contrast in cases of suspected appendicitis.

^cUse dose modulation.

Abbreviations: trans, transaxial; cor, coronal; AAA, abdominal aortic aneurysm; NCCT, noncontrast CT scan.

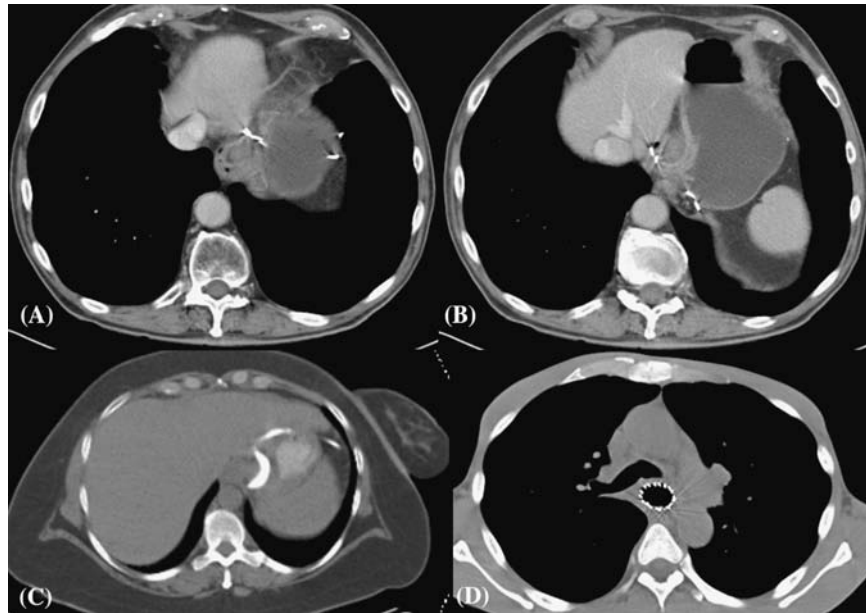


Figure 1 (A) and (B) are two consecutive axial contrast-enhanced CT images from the same patient who has undergone a Nissen fundoplication for gastroesophageal reflux after failing medical therapy. The gastric fundus is wrapped around the distal esophagus, thereby creating an anatomic barrier to reflux, constricting the esophagus at the level of the dysfunctional lower esophageal sphincter limiting gastroesophageal reflux. This may be mistaken for gastric wall thickening, which can be seen in infection, inflammatory, or neoplastic processes. Surgical clips are always present and should hint that there has been prior surgery. Morbid obesity is another potential indication for surgical intervention. In a different patient with morbid obesity and with a history of endometrial cancer (C), a gastric band is visualized on an unenhanced CT scan and is located just below the gastroesophageal junction. The gastric band is placed in an effort to limit the capacity of the stomach. The band is typically placed laparoscopically and can be adjusted using a saline infusion port placed under the skin. The saline infusion catheter is partially imaged while the subcutaneous port is not shown. Occasionally, these bands can migrate and may need revision or replacement. In cases of severe obstruction, endoluminal stents may be placed within the GI tract (esophagus, stomach, colon) to alleviate the obstruction or exclude fistulas, particularly in patients who may not be candidates for surgery. A third patient (D) with esophageal cancer is shown who is status post placement of an endoluminal esophageal stent. Monitoring of the position of the stent is important as they can migrate. *Abbreviations:* CT, computed tomography; GI, gastrointestinal.

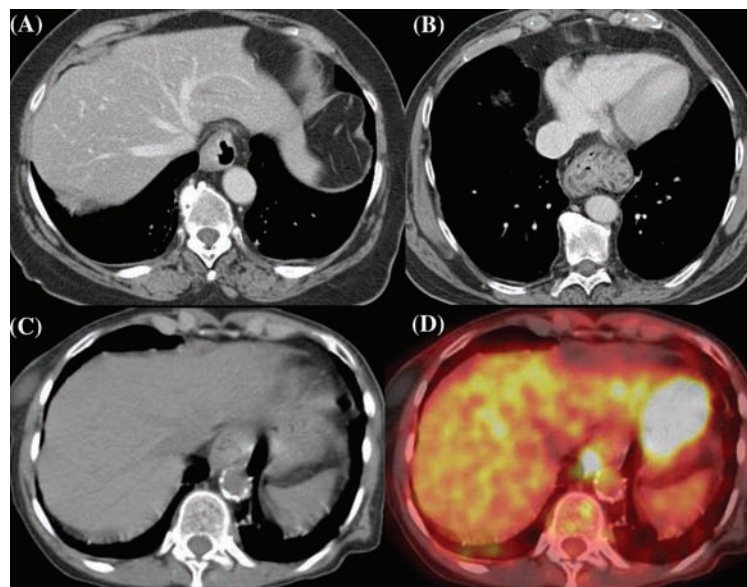


Figure 2 Hiatal hernias. (A) A small hiatal hernia might be confused with esophageal thickening or a mass. (B) Hiatal hernias may be small or more moderate in size as in this case where the gastric folds are evident in the posterior mediastinum due to herniation of a portion of the stomach through the diaphragmatic hiatus. (C) A small hiatal hernia seen here on axial CT corresponds to a site of intense uptake on the fused PET/CT image (D). This could be due to normal physiologic uptake or inflammation. *Abbreviation:* PET/CT, positron emission tomography/computed tomography.

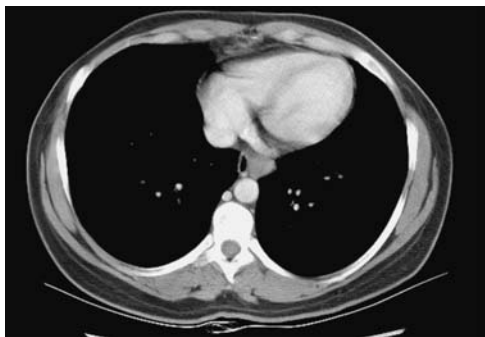


Figure 3 CT scan performed on a 35-year-old man shows a soft tissue density contiguous with the esophagus that proved to be an esophageal duplication cyst. The differential diagnosis includes other soft tissue abnormalities of the esophageal wall, such as a leiomyoma. *Abbreviation:* CT, computed tomography.

time. Unless infected, these are not expected to cause focally increased uptake.

Focally increased FDG activity in the esophagus, which is greater than the level of uptake in the liver and fuses to an abnormality on the CT scan, is suspicious for malignancy. However, other entities that have been described are focal bacterial esophagitis, radiation induced strictures, and Barrett's esophagus (13).

Diffuse

CT has a limited role in the assessment of esophagitis but the diffuse uptake associated with it is a common finding on FDG PET (Fig. 4), especially in oncologic patients. FDG-avid esophagitis may be infectious (14), inflammatory,

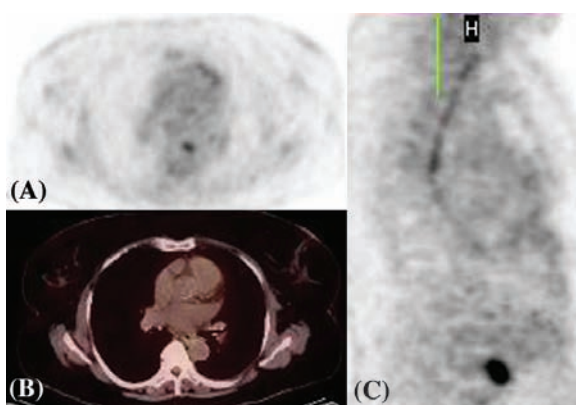


Figure 4 A 46-year-old woman with breast cancer on chemotherapy complaining of dysphagia. PET/CT performed for staging shows mild focal uptake on the axial PET image in the posterior mediastinum (A) that fuses on CT to the distal esophageal wall (B). A sagittal view (C) shows the distribution of activity along most of the length of the esophagus typical of esophagitis. *Abbreviation:* PET/CT, positron emission tomography/computed tomography.

often due to gastroesophageal reflux (15,16), or radiation induced (17). On CT, findings include nonspecific circumferential wall thickening and a target appearance on IV contrast enhancing imaging. The target sign is a layered appearance with enhancement of the mucosa surrounded by a hypodense rim of submucosal edema. Esophageal spasm or dysmotility can also be manifested by symmetric wall thickening and may mimic esophageal cancer. On the metabolic images, coronal or sagittal slices are useful in this setting to fully visualize the extent of uptake and to confirm a linear pattern without discrete foci.

Esophageal varices are most commonly seen in the setting of cirrhosis and portal hypertension. These varices are known as “uphill” varices and surround the distal esophagus and stomach. “Downhill” varices are associated with superior vena cava obstruction and are typically located in the upper and mid esophagus but may be seen in the lower esophagus depending on the level of obstruction. In the setting of underlying cirrhosis and a distal esophageal mass, varices should be considered. Contrast-enhanced CT imaging in the portal venous phase is particularly helpful to demonstrate the enhancement pattern of these tubular or serpiginous venous structures (Fig. 5). Multiplanar reconstructions can permit better appreciation

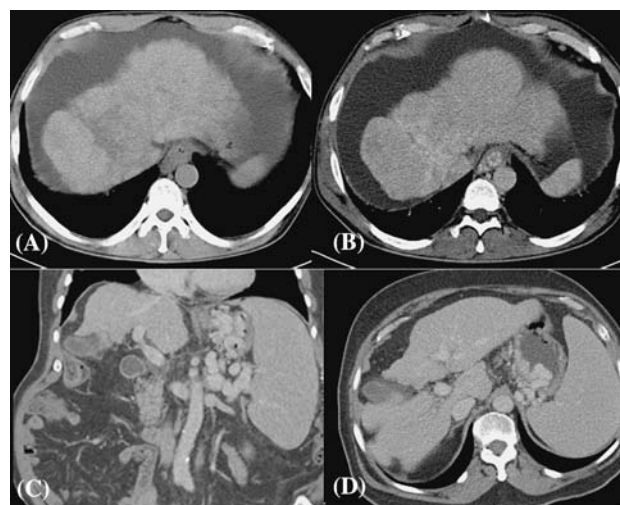


Figure 5 A 53-year-old man with cirrhosis with confluent fibrosis at the dome of the liver and portal hypertension. Noncontrast CT through the liver and distal esophagus (A) shows the nodular contour of the liver and soft tissue thickening around the esophagus. Following administration of nonionic IV contrast, (B) this apparent esophageal “thickening” corresponds to “uphill” varices related to portal hypertension. Coronal reformatted (C) and axial images show additional findings of cirrhosis and portal hypertension including atrophy of the right hepatic lobe and lateral segment hypertrophy, gastric varices, and splenomegaly (D). *Abbreviation:* CT, computed tomography.

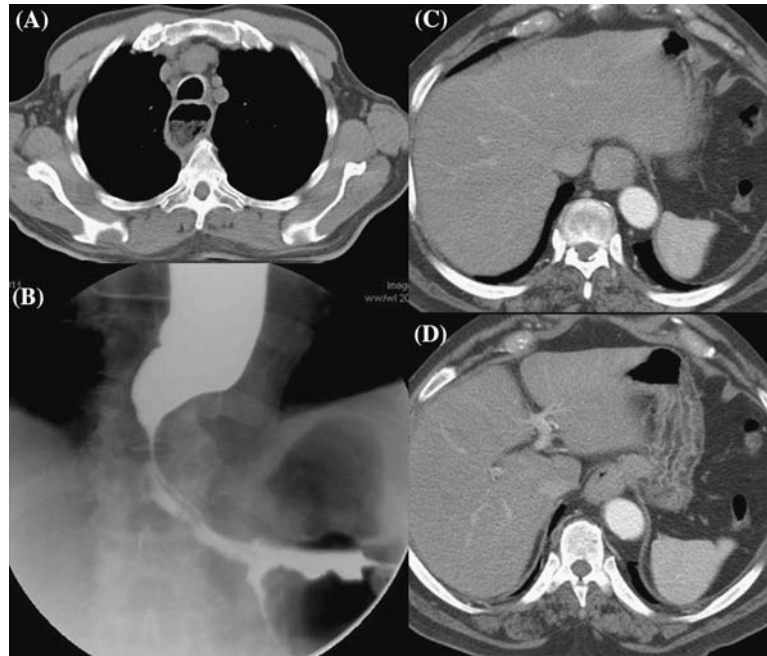


Figure 6 (A) axial unenhanced CT image through the upper esophagus shows dilatation of the esophagus with retained secretions and debris in this patient with primary achalasia. (B) In another patient (B–D) an image from an upper GI study (B) shows dilatation of the distal esophagus with narrowing at the GEJ, so-called pseudoachalasia, due to a GEJ adenocarcinoma. Axial contrast-enhanced CT images through the esophagus (C) and the cardia of the stomach (D) of the same patient demonstrates abnormal esophageal wall thickening and a soft tissue mass extending to the GEJ. *Abbreviations:* GI, gastrointestinal; GEJ, gastroesophageal junction; CT, computed tomography.

of the course of the vessels, helping to distinguish between solid masses and vascular channels.

Achalasia may be primary or secondary. Primary achalasia is caused by loss of normal function of the myenteric plexus of the esophagus with impaired relaxation of the lower esophageal sphincter. This results in esophageal dilatation and stasis with fluid, debris, and retained secretions accumulating in the esophagus. There is typically an abrupt distal tapering or “beak-like” narrowing at the GEJ (Fig. 6). Focal, less than 1 cm smooth circumferential wall thickening at the level of narrowing may be present.

Secondary achalasia is due to the presence of a neoplasm at the GEJ and may involve a longer segment of the esophagus and is associated with asymmetric narrowing and nodularity.

Primary Esophageal Cancer

Esophageal cancer is the sixth most prevalent cancer in men, and the ninth most prevalent in women worldwide, with a higher prevalence in the developing world (18). However, the prevalence of adenocarcinoma of the esophagus is on the rise particularly in the United States. The incidence has quadrupled between 1973 and 2002 while squamous cell carcinoma declined by 30% in that same period (19).

Alcoholism and smoking are both risk factors for esophageal cancer (19). Adenocarcinoma is associated with chronic gastroesophageal reflux disease (GERD) and typically arises within the distal esophagus (19). It may be seen in 10% of cases with Barrett’s metaplasia (20). Barrett’s metaplasia itself can be FDG avid and may show segmental uptake (20) but may also be focal (13) and possibly confused with adenocarcinoma.

It is difficult to distinguish between adenocarcinoma and squamous cell carcinoma on CT imaging. In addition, on PET the level of FDG uptake is similar in adenocarcinomas and squamous cell carcinomas and cannot be reliably differentiated using SUV measurements (21). While the morphologic appearance of squamous cell carcinoma and adenocarcinoma may be similar, squamous cell tends to involve the upper or mid esophagus, while adenocarcinoma tends to involve the GEJ and is more likely to invade the cardia or fundus of the stomach.

Delineation of esophageal neoplasms on CT requires adequate esophageal distention and IV contrast. Early-stage esophageal cancer may not be appreciated on CT imaging, or may present with only minimal wall thickening, less than 5 mm. Alternatively, early-stage tumors may present as a small intraluminal polypoid mass (22). Differentiating between early esophageal malignancy and benign tumors, infectious or inflammatory processes

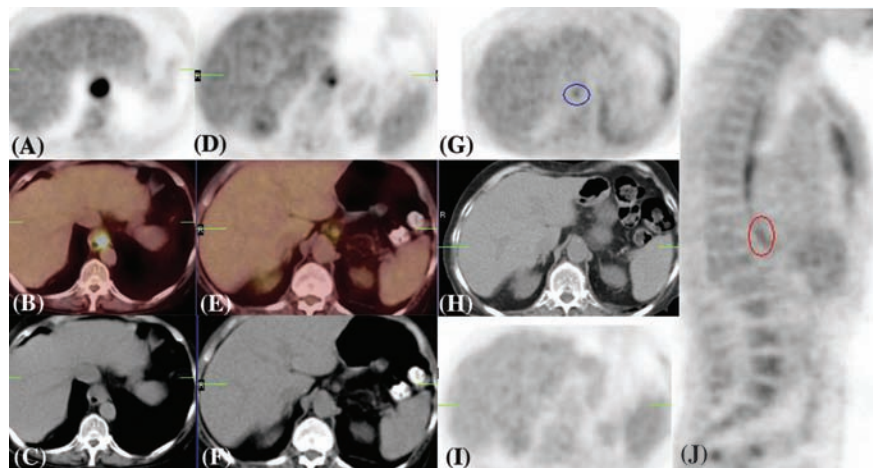


Figure 7 A 61-year-old man with dysphagia and a newly diagnosed distal esophageal carcinoma. (A) Transaxial FDG image through primary tumor from the PET/CT performed for staging shows intense uptake (SUV 12.3) that fuses (B) to the eccentric soft tissue density thickening in the esophageal wall on the corresponding axial CT image (C). More inferiorly, increased FDG uptake is seen (D) fusing (E) to a metastatic gastrohepatic lymph node seen clearly on the corresponding CT (F). The patient was treated with radiation and three months later, the activity in the primary tumor (G) has decreased (SUV 2.3), the node is no longer visible on CT (H), and the activity in the lymph node is gone (I). A sagittal PET slice demonstrates diffuse activity in the esophagus and at the anterior edge of the mediastinum (J). *Abbreviations:* PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value.

may be difficult. Asymmetric wall thickening, nodularity and/or ulceration are more indicative of malignancy (Fig. 7). Varicoid carcinoma, which spreads along the lymphatics and vasculature, may mimic varices and is best assessed with endoscopy or under fluoroscopy. In the absence of anatomic abnormality, focally intense uptake on FDG PET still raises concern for neoplasm.

PET detects primary tumors with higher sensitivity than CT (Table 2), 95% to 100% versus 81% to 92%, respectively, as shown in multiple studies (23–30). False negative results, however, are secondary to small tumor volume (24,31) and well-differentiated tumors, which tend to be less FDG avid (31).

Tumor (T) Staging

T staging of esophageal cancer depends on the thickness of the primary tumor and the depth of invasion (Table 3). PET/CT has the resolution to detect tumors that extend to

the submucosa, but in general is unable to distinguish those involving only the mucosa (31,32). Currently, no clear relationship exists between SUV uptake and tumor depth (21,30).

Table 3 TNM Staging of Esophageal Cancer Based on UICC Criteria

T staging	
Tx	The tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ
T1	The tumor invades the lamina propria or submucosa but does not invade the muscularis propria
T2	The tumor invades, but does not extend beyond, the muscularis propria
T3	The tumor invades the periesophageal tissues but does not invade adjacent organs
T4	The tumor invades adjacent structures
N staging	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
M staging	
Mx	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1a	Metastasis to cervical or celiac lymph nodes
M1b	Other distant metastases

Notes: N, regional lymph nodes; M, distant metastases.
Source: From Ref. 327.

Table 2 PET Detection of Esophageal Primary Tumors

Author (Ref.)	PET sensitivity	CT sensitivity
Flanagan (1997) (23)	100%	92%
Block (1997)(24)	96.5%	
Luketich (1997)(26)	97%	
Rankin (1998)(27)	100%	96%
Yeung (1999)	99%	
Kato (2005) (31)	80%	

More advanced tumors may demonstrate a more pronounced, greater than 5 mm wall thickening, ulceration, or an irregular mass. T3 and T4 tumors extend beyond the muscularis propria into the periesophageal fat, adjacent mediastinal structures, and may also be associated with regional lymphadenopathy. Necrotic portions of the tumor will appear photopenic on FDG PET. CT is helpful for differentiation between tumors confined to the esophagus and those that have extended beyond the esophagus. Tumors that extend beyond the esophagus likely are not surgically resectable.

Esophageal cancer typically spreads into adjacent structures such as the trachea and bronchi, aorta and pericardium by direct extension. Periesophageal extension may be manifested by soft tissue stranding in the periesophageal fat. The posterior wall of the trachea or the bronchi may be invaded by tumor. Loss of a fat plane between the tumor and the trachea or bronchi is not sensitive for invasion; however, displacement or indentation on the trachea or bronchus is highly suggestive of tumor invasion (22). Aortic invasion is rare, but if the tumor becomes contiguous with the aorta and surrounds greater than 90° of its circumference then invasion is likely. Pericardial invasion is suspected on the basis of loss of normal pericardial fat planes and development of mass effect on the heart. FDG PET may not be able to distinguish local invasion from locoregional nodal metastases (30,31).

Lymph Nodes (N) Staging

Survival in esophageal cancer is related to the extent of lymph node involvement (33), and, therefore, accurate nodal or N staging is critical to both the treatment plan as well as to the overall prognosis (Table 4). Regional lymph nodes for tumors of the upper esophagus include supraclavicular, internal jugular, cervical, and periesophageal

(34). For tumors arising in the mid-thoracic esophagus, lymph node metastases are usually seen in the paratracheal, subcarinal, and periesophageal region, while tumors near the GEJ may be associated with diaphragmatic, gastrohepatic ligament, and periceliac lymphadenopathy (Fig. 7).

Size criteria for lymph nodes metastases on CT are nonspecific. While a diameter of 10 mm is considered abnormal on CT, many metastatic lymph nodes are actually smaller (26). Lymph node size does not correlate well with frequency of metastases (35). Endoscopic ultrasonography (EUS) has been found to be more accurate than CT in the evaluation of locoregional lymph node involvement, but both modalities are limited in detection of disease in normal-size lymph nodes. A study comparing the sensitivity, specificity, and accuracy of PET with CT and histopathological results from lymph node dissection demonstrated that PET has the same specificity (94–97%) as CT, but significantly greater sensitivity (52% vs. 15%), and accuracy (84% vs. 77%) (36). It has been shown that FDG PET has the potential to upstage or downstage lymph nodes compared with CT (31). EUS, however, is significantly more sensitive than PET in the detection of regional lymph node involvement (81% vs. 33%), but less specific (67% vs. 89%) (30). The combination of EUS and CT is more sensitive than PET, but again, less specific (37). Overall, for N staging, PET, EUS, and CT are less sensitive and specific than extensive lymph node dissection, which remains routine in patients who are considered surgical candidates after imaging.

Staging of Distant Metastatic Disease (M Staging)

In the TNM staging of esophageal cancer, the most profound impact of PET/CT is in the detection of distant metastatic disease (Table 5) and in the direction of biopsy

Table 4 PET and CT Detection/Staging of Regional Lymph Node Metastases

Author (Ref.)	PET sensitivity/ specificity/accuracy	CT sensitivity sensitivity/ specificity/accuracy	PET plus CT sensitivity/ specificity/accuracy
Flanagan (1997) (23)	72%/82%/76%	28%/73%/45%	
Block (1997) (24)	45% (sens)	21% (sens)	67% (sens)
Luketich (1997) (26)	45%/100%/48%		
Rankin (1998) (27)	21% (sens)	47%(sens)	58%
Yeung (1999) (29)	28%/99%/79%	25%/98%/77%	
Kim (2001) (36)	52%/94%/84%	15%/97%/77%	
Lerut (2000) (37)	22%/91%/48%		
Himeno (2002) (32)	42%/100%/92%		
Kneist (2003) (328)	6–42%/94–100%/59–82%		
Rasanen (2003) (329)	37%/100%/63%		
Kato (2005) (31)	55%/90%/72%	23%/97%/91%	

Abbreviation: Sens, sensitivity.

Table 5 PET and CT Detection of Distant Esophageal Metastases

Author (Ref.)	PET sensitivity/specificity/ accuracy	CT sensitivity sensitivity/ specificity/accuracy	PET plus CT sensitivity/ specificity/accuracy
Block (1997) (24)		45% (sens)	82% (sens)
Luketich (1997) (26)	88%/93%/91%		
Luketich (1999) (38)	69%/93%/84%		
Flamen (2000) (30)	74%/90%/82%	41%/83%/64%	
Kneist (2003) (328)	35% (sens)/87% (spec)		
Rasanen (2003) (329)	47%/89%/74%		
Kato (2005) (31)	94% (sens)	67% (sens)	

Abbreviation: Sens, sensitivity; Spec, specificity.

to the anatomic site that may be sampled with minimally invasive procedures. Distant metastatic disease precludes patients from surgery with curative intent because of the high morbidity and poor outcomes of those with disease in distant organs, in favor of palliative, nonsurgical management. The more common sites of metastases in esophageal carcinoma, besides distant lymph nodes, are liver, bone, and lung (31).

PET is demonstratively superior to CT in the detection of distant metastases in these sites (23–26,38), although tiny lung metastases will be seen with greater sensitivity on CT (31). A prospective study showed the sensitivity and specificity of PET in the detection of distant disease to be 74% and 92% in comparison with 41% and 83% for CT and 42% and 94% for EUS (38). More recently a prospective cooperative study by the American College of Surgeons Cooperative Group found that PET upstaged disease to M1 in 4.8% to 14.3% if unconfirmed PET findings that were accepted by surgeons were included (39). In general, PET tends to upstage disease; however, because of the potential for false positives or false negatives, histologic confirmation of metastatic disease should be obtained prior to confirmation of staging that could deny a patient potentially curative treatment (39). Fortunately, PET/CT can facilitate this process by indicating the area of most increased FDG activity in relation to anatomic landmarks, thus ensuring appropriate biopsy of the lesion in question.

Prognostic Indicators

The level of FDG uptake in tumor at presentation has been found to be predictive of overall prognosis; and an SUV greater than 7.0 prognosticates a poorer outcome than in patients with less FDG uptake (21). Furthermore, PET evidence of metastatic disease, local or distant, also indicates overall survival (38).

FDG PET has been evaluated to determine its ability to predict tumor response to initial therapy or overall response to neoadjuvant therapy, in comparison with

anatomical imaging techniques. A study performed, which examined patients who underwent FDG PET scan before and 14 days after the induction of neoadjuvant chemotherapy, demonstrated that a decrease in the FDG uptake by 35% on PET was able to predict responders (i.e., those whose tumor length and wall thickness decreased by >50% 3 months after completion of treatment by endoscopy and conventional imaging). This change in SUV had a sensitivity of 93% and a specificity of 95% (40). More recently, this degree of decrease in SUV was shown to be associated with a 44% histologic response rate and a three-year survival of 70% (41). Nonmetabolic responders in this study showed only a 5% histologic response rate at surgery following neoadjuvant therapy and had a three-year survival rate of only 35%. The two-year disease-free survival of patients following induction therapy and esophagectomy was 38% and overall survival was 63% when the SUV of the tumor decreased less than 60% between the initial study and the posttherapy scan. Those values increase to 67% disease-free survival and 89% survival when the SUV change was greater than 60% (42). Four to six weeks after the completion of radiation therapy, a decline of SUV to less than 4 on PET, a decrease of the extent of the tumor to less than 1 cm on EUS, and a thickness of less than 14.5 cm predicted a better response to therapy in another series of patients treated with combined chemotherapy and radiation neoadjuvantly (43). For this SUV criterion, the sensitivity, specificity, and accuracy of predicting a poor response was 62%, 84%, and 76%, respectively (43). In terms of accuracy, PET was better than EUS or CT for predicting treatment response. Overall, a decrease in FDG activity in the primary tumor is identified as a positive response to therapy, with no change or even an increase in accumulation of radiopharmaceutical in less effective treatment. It is the decline in FDG uptake that best correlates with absence of recurrent disease (41). Furthermore, it has been suggested that the number of PET positive lymph nodes in patients with squamous cell carcinoma will predict overall survival (44).

Other Malignant Tumors of the Esophagus

Other malignant tumors to consider include: lymphoma, spindle cell carcinoma, which usually presents as a bulky polypoid intraluminal mass, leiomyosarcoma, malignant melanoma, and Kaposi's sarcoma. Primary malignant melanoma is rare, representing less than 0.5% of all esophageal malignancies, and usually also presents as a polypoid intraluminal mass (45). More often melanoma metastasizes to the GI tract, typically the small bowel, but can also spread to the stomach, esophagus, and colon. Differential diagnosis of an intraluminal-filling defect should include spindle cell, leiomyosarcoma, other benign tumors described above, as well as impacted food or debris.

Metastatic disease to the esophagus most commonly spreads contiguously from gastric adenocarcinoma and can lead to obstruction. Lung, breast cancer, melanoma, and renal cell carcinoma may also spread to the esophagus and may mimic a benign stricture.

Recurrence

In esophageal cancer, early detection of recurrence, which is common, may allow for treatment with the goal of

extending disease-free survival or even with curative intent. Conventional anatomic imaging faces the challenge of differentiating recurrence from posttherapy changes, such as scarring and inflammation (Fig. 8).

Postoperative Changes

Familiarity with the postoperative and posttreatment appearance of the esophagus is important, as disease burden in assessing response or recurrence may be overestimated. Esophagectomy may be performed with anastomosis of the remaining esophagus to the stomach, which will be pulled into the chest (Fig. 9). This can mimic a hiatal hernia. Complications of such a procedure include anastomotic leak, hemorrhage, and subphrenic abscess (Fig. 10). Colonic or small-bowel interpositions may also be performed and have a more unusual appearance. Colonic interpositions may be substernal or follow the normal course of the esophagus in the posterior mediastinum (Fig. 11).

Postradiation changes in the esophagus may include dysmotility, mucosal edema, and ulceration and are not readily distinguished from other esophagitides. Inflammation and fibrosis related to postsurgical or postradiation changes may lead to wall thickening; but typically, there

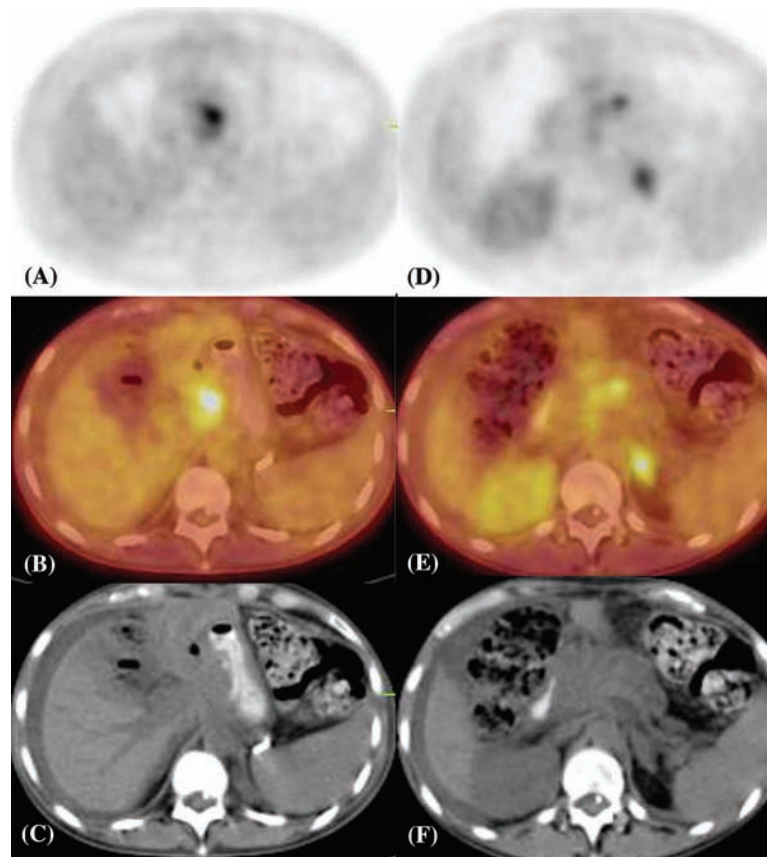


Figure 8 65 year old man with (A) an FDG avid distal primary esophageal carcinoma evident on (B) fused images and on (C) CT images. Post-radiation images demonstrate a focus of persistent uptake (D) on PET scan which is most consistent with residual disease within diffuse inflammatory type changes. In addition, a new FDG avid left adrenal metastasis is seen on the (E) fusion images and also as enlargement on the (F) CT.

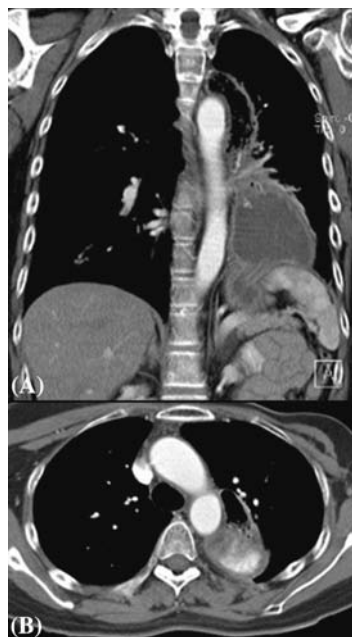


Figure 9 A 73-year-old woman with a history of esophageal cancer treated with resection and a gastric pull through. (A) Coronal reformat and (B) axial contrast-enhanced CT images show the pulled up stomach in the posterior left mediastinum. *Abbreviation:* CT, computed tomography.



Figure 10 A 64-year-old man who underwent esophagectomy with gastric pull through complicated by a suture dehiscence. The CT shows extravasated oral contrast collecting in the pleural space (white arrow). The gastric pull up (white arrowhead) is seen adjacent. *Abbreviation:* CT, computed tomography.

is smooth and symmetric circumferential thickening suggestive of a benign process. In the setting of radiation-induced esophagitis, there may be adjacent mediastinal fibrotic changes. In the relatively early stages, diffuse uptake will be seen on PET.

Wall stents may be placed within the esophagus as palliative measures to relieve obstruction or to treat tracheoesophageal fistulas (Fig. 1). These radiopaque stents are readily seen on scout radiographs. Complications include stent migration and compression of adjacent bronchi or vascular structures (46). Tumor ingrowth may also be seen in uncovered metallic stents.

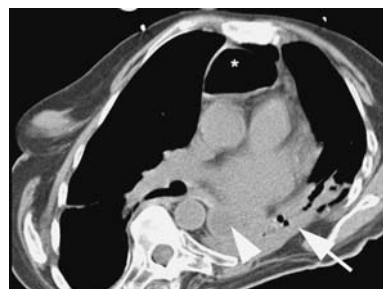


Figure 11 A 54-year-old woman with scoliosis status post-colonic interposition for esophageal cancer. The scan shows the substernal colonic interposition (*) with retained secretions in the native esophageal stump (white arrowhead) and left lower lobe consolidation (white arrow).

Increased metabolic activity indicating viable tumor may be identified on FDG PET prior to visible structural alterations on anatomic imaging. Again, the ability to determine increased uptake allows PET a high degree of accuracy in the detection of recurrent disease (29).

STOMACH AND DUODENUM

Normal Findings

FDG uptake in the stomach may be diffusely increased, especially in the nondistended stomach, and the use of oral contrast as well as the distention of the gastric walls, will help avoid this pitfall (47). Although there may be elements of heterogeneity, in general, a physiologic pattern of activity has few or no discrete foci fusing to the gastric walls. Increased activity may be seen at the GEJ and in the absence of a CT abnormality, is also likely physiologic and secondary to normal muscular contraction of the lower esophageal sphincter (48). This may be slightly but not significantly increased in the setting of GERD (48). An analysis of the pattern of gastric uptake suggests that in patients without a history of esophagogastric disease, a gastroesophageal SUV maximum less than 4 is less likely to represent neoplasm. If the SUV is greater than 4, further evaluation with endoscopy may be indicated (48).

The appearance of the stomach and duodenum on CT is variable. The stomach may be divided into segments. The cardia is the region of the GEJ, the fundus is the out-pouching above the GEJ, to the left of the GEJ. The body is the central portion extending from the cardia to the incisura angularis or the region of acute angle seen at the junction of the lesser curve and the antrum. The antrum is the distal portion of the stomach to the level of the pylorus. The pylorus is located at the junction of the stomach and duodenum. The pyloric canal may appear thick walled relative to the stomach and is variable in appearance. The duodenal bulb is the first portion of the

duodenum, followed by the second portion or vertical descending portion. The common bile duct (CBD) and pancreatic duct drain via the ampulla of Vater into the medial aspect of the second portion of the duodenum. The third or horizontal portion passes between the superior mesenteric vessels and the aorta and inferior vena cava (IVC). The fourth or ascending portion extends to the left side of the aorta to the ligament of Treitz where it turns vertically and becomes the jejunum. Normal gastric wall should not exceed 5 mm and normal duodenum should not exceed 3 mm, but adequate distention is necessary to determine the diameter of the wall.

Malignancy

By far the most common malignancy of the stomach is adenocarcinoma. Other tumors to be aware of include gastric carcinoid, non-Hodgkin's lymphoma, GIST, Kaposi's sarcoma and metastatic disease from lung, breast, melanoma, esophageal, and colon primaries.

PET has increased levels of uptake in lymphoma of the stomach, with a higher SUV associated with high-grade malignancy and lower SUV consistent with low-grade tumors (see chap. 17 "PET/CT in Evaluating Lymphoma"). Similarly, in GIST involving the stomach, high-grade tumors are FDG avid and PET/CT can be used to follow treatment and detect recurrence (49). The use of PET/CT in the evaluation and staging of gastric cancer is not clearly established, but studies indicate that there may be an evolving role for this imaging modality.

Gastric Cancer

On CT imaging, a focal, eccentric or enhancing wall thickening raises the possibility of gastric cancer (50). Gastric wall thickening on CT imaging of 2 cm or more has only a moderate sensitivity for detection of gastric cancer (50%) with a high specificity (50). If 1 cm thickening is used for the criterion, sensitivity increases to 100% but specificity will decrease to 36% (50). Like esophageal cancer, the appearance of early stage gastric adenocarcinomas can be subtle. T1 tumors (Table 6) may present with focal wall thickening, irregularity or a mass with preservation of the outer layer of the gastric wall (Fig. 6). Size and morphology can be variable ranging from polypoid, fungating masses to irregular, broad-based ulceration masses. T2 tumors may be present with focal or diffuse thickening of the gastric wall with transmural involvement with a preserved perigastric fat plane (51). T3 tumors are associated with infiltration of the perigastric fat. Primary lesions may be irregular or nodular (Fig. 12). T4 tumors extend into adjacent structures obliterating fat planes and directly invading contiguous

Table 6 TNM Staging of Gastric Carcinoma

T staging	
T1	Tumor limited to lamina propria or submucosa
T2	Tumor invading muscularis propria or the subserosa
T3	Tumor penetrates the serosa and perigastric tissue, but spares adjacent structures
T4	Tumor invading adjacent organs
N Staging	
N0	No evidence of lymph node involvement
N1	Involvement of perigastric lymph nodes within 3 cm of the primary tumor
N2	Involvement of lymph nodes farther than 3 cm from the primary or in left gastric, common hepatic, celiac, or splenic lymph nodes
M staging	
M0	No evidence of distant metastases
M1	Evidence of distant metastases.

organs. As with esophageal tumors, dynamic contrast-enhanced imaging may be helpful, but depth of invasion is better assessed by endoscopic ultrasonography (US). Scirrhous gastric carcinoma is an unusual infiltrating form of adenocarcinoma that can affect the stomach and colon. A discrete mass may not be apparent; instead there is circumferential infiltration by tumor leading to wall thickening and intraluminal narrowing secondary to fibrosis with loss of normal peristaltic activity (52). In the stomach, it can present with linitis plastica, which may be difficult to appreciate on a nondynamic study such as CT. Differential diagnosis includes scirrhous metastases from lung or breast cancer as well as lymphoma (Fig. 12), Crohn's disease, gastritis, sarcoidosis, and amyloidosis. Unfortunately, CT criterion such as size, shape, and enhancement pattern of various gastric lesions are variable and, therefore, are not reliable for diagnosis as there is significant overlap in imaging findings. Other benign disease entities to consider and not to confuse with gastric carcinoma on CT include gastritis. CT is typically insensitive to the subtle changes of gastritis. However, gastritis may present as fold thickening (Fig. 12). Submucosal low attenuation due to edema, resulting in a layered or target appearance may be present. Varices may also mimic tumors as in the esophagus. Isolated gastric varices and splenomegaly may be seen with splenic vein thrombosis usually because of pancreatitis or pancreatic neoplasm. Peptic ulcer disease is typically not appreciated on CT unless there is deep ulceration or perforation with extraluminal gas or air fluid collections.

On FDG PET, inflammatory conditions including gastritis, subclinical infection with *Helicobacter pylori*, or secondary to effects of chemotherapy, usually demonstrate diffusely increased uptake that fuses to the wall on CT scan. Clinical correlation is important in stratifying

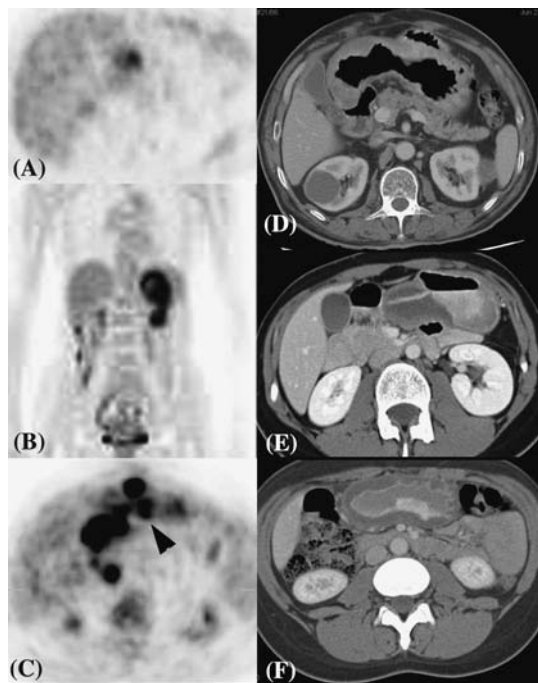


Figure 12 Causes of gastric thickening. (A) Focal uptake in the gastric antrum on FDG PET found to be gastric adenocarcinoma on biopsy. (B) Diffuse uptake in the gastric wall on FDG PET proved to be a diffusely infiltrating gastric carcinoma. (C) Focal uptake in the gastric antrum (arrowhead) with liver metastases and portal lymphadenopathy on FDG PET in a patient with gastric adenocarcinoma. (D) Diffuse and irregular thickening of the gastric wall on CT is secondary to non-Hodgkin's lymphoma. (E) Localized, but smooth and concentric benign thickening of the gastric antrum on contrast-enhanced CT scan due to focal, severe gastritis. (F) Diffuse gastric thickening with contrast enhancement of the mucosa is secondary to gastritis. *Abbreviations:* PET, positron emission tomography; CT, computed tomography.

the differential diagnosis in that pattern of radiopharmaceutical distribution. Pattern and SUV findings in inflammation do not preclude infiltrative malignant processes.

In addition to a thorough history and physical, blood counts and blood chemistries, abdominal CT, endoscopy, and pelvic ultrasound or CT, National Comprehensive Cancer Network (NCCN) staging guidelines now include PET/CT for patients with more than T1 tumors and no clear-cut evidence of distant metastases (53).

Primary Tumor (T) Staging

Studies have demonstrated a sensitivity of 93% (54) to 94% (55) for PET in the detection of gastric cancer, which is similar to the sensitivity of CT. False negative results are again related to small tumor size and histopathologic type. A significant difference in sensitivity has been shown in PET's ability to identify early gastric cancer

(63%) as opposed to advanced gastric cancer (98%) (55). Furthermore, a higher mean SUV (7.7) (55) is associated with the tubular adenocarcinoma type of malignancy. Decreased FDG activity is seen in mucinous and signet ring cell tumors (SUV mean 4.2) (55), which is a function of both the lower expression of GLUT-1 transporters on the cell membrane surface of mucinous and signet ring cell tumors (56). Physiologic background FDG activity in the stomach may obscure these tumor types. However, GLUT-1 expression appears to increase with depth of invasion of tumors and with progression of disease to higher stages (56). Increased FDG uptake is not unexpectedly associated with increasing depth of invasion, larger primary tumors, and more lymph node involvement (57). Furthermore, patient survival appears significantly worse for patients whose primary tumor has an SUV of greater than 4, compared with those with SUV less than 4 (57). Thus, FDG uptake is expected to increase as the aggressivity of gastric carcinoma increases.

Lymph Node (N) Staging

Lymph node metastases may initially involve the perigastric nodes, but regional lymph nodes along the celiac artery and its branch vessels may occur with some frequency as well. In the detection of local lymph node involvement, PET demonstrates a lower sensitivity than CT (56% vs. 78%) (55), but a higher specificity (92% vs. 62%) (55). The overall accuracy of PET and CT in the detection of malignancy in local and distant lymph nodes is not significantly different. However, the combination of PET and CT increased the accuracy of staging (55). PET faces a challenge in distinguishing between N0 and N1 disease because of the intense uptake from the primary malignancy, which may obscure FDG accumulation in discrete lymph nodes adjacent to the tumor. In addition, studies suggest a correlation between the FDG avidity of the primary tumor and the likelihood of lymph node involvement; the higher the SUV, the presence of metastases to lymph nodes was more likely (55,57).

Distant Metastases (M) Staging

Distant supraclavicular and axillary lymph nodes may be seen. Peritoneal seeding and omental metastases will be present in advanced disease. Metastases to the ovaries may be seen with signet-ring adenocarcinoma of the stomach sometimes referred to as Krukenberg's tumors. On CT, Krukenberg's tumors can be solid, with cystic components or primarily cystic. Solid components will show enhancement. They are slightly more likely to be solid than ovarian cancer (58).

PET has shown a low sensitivity in comparison with CT in patients with peritoneal dissemination (54,59), possibly due to the diffuse distribution of malignant

cells within fibrotic changes, which does not permit adequate accumulation of detectable FDG. Overall PET may be useful in locating metastases in the liver, lungs, and lymph nodes, but is less so in identifying osseous metastases and peritoneal carcinomatosis (60) where spatial resolution becomes a limiting factor.

Therapeutic Approaches

For T1 tumors without evidence of distant metastases, surgery, either laparoscopic or open surgery, is recommended. Once tumors progress beyond T1, but still appear resectable, neoadjuvant chemotherapy is usually interposed between initial staging and surgery. Changes in SUV have been shown to reflect histopathologic response to neoadjuvant chemotherapy (61). Unresectable primary tumors are treated either with concurrent radiotherapy and chemotherapy, or with chemotherapy alone. The presence of distant metastatic disease requires salvage therapy, which will depend on the performance status of the patient, but when possible will include chemotherapy, either standard or experimental (53). For tumors more advanced than T1, adjuvant chemotherapy or combined chemoradiation may be indicated.

Postsurgical changes on CT following gastrectomy may vary depending on the procedure. Patients may undergo total or subtotal gastrectomy, esophagogastrectomy with a gastrojejunostomy typically performed with Roux en y anastomosis, or Billroth II reconstruction. Roux en y anastomoses require division of the jejunum with formation of a proximal afferent loop through which pancreaticobiliary secretions drain. This loop is then connected to more distal jejunum beyond the level of the gastrojejunostomy via an enteroenterostomy. Postoperatively, biliary air may be seen (62). Also, surgical folds may mimic masses (62). Complications include anastomotic leaks, ulceration, abscess, hematoma, hernias, bowel obstruction, and recurrence. The CT appearance of afferent loop obstruction is typically a transversely oriented, dilated loop of bowel in the middle of the abdomen (62). Incisional and hiatal hernias occur postgastrectomy (62).

Suspected Recurrence

Surveillance after curative intent therapy includes clinical laboratory blood tests, chest radiograph, abdominal CT, and pelvic imaging in women, or a PET/CT in addition to blood work (53) according to NCCN guidelines, but blood work may be sufficient with imaging reserved for symptomatic patients (63). Tumor markers, either carcinoembryonic antigen (CEA) or CA19-9 have only moderate sensitivity when used separately, but combined, the sensitivity is quite high (64). The use of more expensive imaging studies to evaluate for recurrence is somewhat

controversial and balances the emotional needs of the patients with the current reality that even early recurrences are incurable (64). Nonetheless, recurrences tend to occur in one of four patterns: gastric bed or regional lymph nodes with direct extension, peritoneal recurrence, liver metastases, or more distant metastases (64). The liver is the most common site of hematogenous spread, but lung, adrenal, kidney, and osseous metastases also occur (62).

CT evaluation should be performed with adequate gastric distention and IV contrast (62). Recurrences in the gastric stump are more common than at the anastomosis and will appear as wall thickening or a polypoid mass (65). Soft tissue masses in the region of the pancreas with isoattenuation or heterogeneity after contrast may be seen as well as abdominal wall soft tissue at the incision (65). Peritoneal seeding presents on CT as fluid collections, nodules, or omental or mesenteric beading or stranding (62).

A small study, which used FDG PET to examine patients with suspected gastric cancer recurrence following surgery, demonstrated a sensitivity of 70%, a specificity of 69%, a positive predictive value of 78%, and a negative predicted value of 60% (66) in the detection of recurrent disease. In addition, they found a longer survival in patients with a negative PET scan (21.9 ± 19.0 mo) versus those with a positive PET scan (9.2 ± 8.2 mo) (66). In another small series of 16 patients, PET was concordant with CT in 12 demonstrating the recurrence, but showed peritoneal recurrence unsuspected on other studies in three patients (59) and unconfirmed recurrences in two patients. In recurrence with metastases to the liver, FDG PET has shown in a meta-analysis to have a higher sensitivity (90%) than either CT (70%) or MRI (71%) (1). PET/CT in comparison with CT alone has shown much greater sensitivity for mediastinal lymph node recurrences (67). Since in the past FDG PET has been particularly helpful when other imaging studies are equivocal (64), PET/CT may provide more sensitive and specific information in patients with suspected recurrent gastric cancers (Fig. 13).

GISTs

GISTs arise from mesenchymal cells. Greater than 90% of GISTs are located in the stomach and small bowel, more commonly in the jejunum or ileum but can occur anywhere in the GI tract. These lesions may be submucosal or subserosal, and are often heterogenous following administration of contrast. The more aggressive and recurrent tumors tend to be more irregular in shape and inhomogeneous (68). Necrosis, cystic foci, calcification, fistula, and/or peritoneal carcinomatosis may be seen with more aggressive tumors. GISTs can invade adjacent organs similar to adenocarcinoma or metastasize hematogeneously to the liver and lung. The most common sites of metastasis are

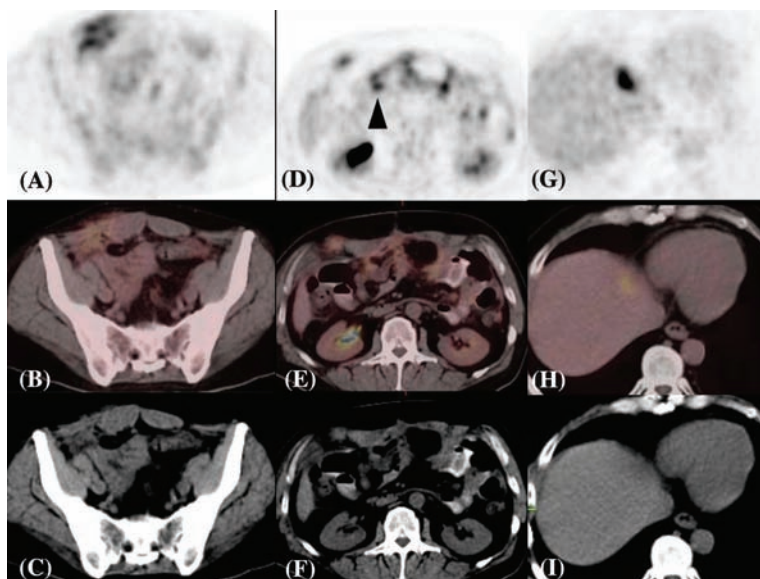


Figure 13 PET/CT performed in a 46-year-old woman with metastatic gastric cancer. (A) FDG PET shows increased activity that (B) fuses to right lower quadrant peritoneal and abdominal wall metastases on (C) unenhanced CT. In the same patient, at the level of the kidneys in the mid abdomen FDG PET (D) demonstrates metastatic foci in the anterolateral abdominal wall and the wall of the transverse colon (arrowhead) implant activity as seen on fused images of the FDG PET (E) and unenhanced CT (F). In the liver, a focus is seen on the PET (G) that fuses (H) to a faint irregular hypodensity on the unenhanced contrast CT (I). *Abbreviations:* PET, positron emission tomography; CT, computed tomography.

the omentum and the liver (69). In a series of 54 patients with GIST undergoing staging, CT had a 93% sensitivity on a per lesion basis compared with 86% for FDG PET (70). Specificity of CT was 100% compared with 98% for PET (70). These differences were not statistically significant. However, it has been recognized that not all GISTs are FDG avid, in one series of 34 patients, sensitivity of PET on a per patient basis was 79% (71). Thus, in another series, contrast-enhanced CT identified 45% more lesions than PET alone (71). Furthermore, inline PET/CT facilitates identification of lesions in the majority of patients and provides a better assessment of surgical respectability (71). It has been suggested that the intensity of uptake of FDG correlates with the malignant potential and aggressiveness of a GIST (49,72).

Although surgery in the past was the first line therapy for GIST, GISTs that express the C-kit mutation may be amenable to imatinib therapy. Surgery is now reserved for imatinib resistant patients, for palliation of symptoms or hemorrhage (69). Surgery may also play a role once imatinib therapy has achieved its maximum tumor response (69).

FDG PET plays a more important role in following patients being treated with imatinib although it may also be useful in monitoring for recurrence in surgically treated patients (Fig. 14). It is becoming clear that PET predicts response to imatinib better than CT at two months (70,73) and at one week (74,75), (Table 7). The criteria for

metabolic response seen to predict response to therapy varies across the literature. Choi et al. suggested that the decrease should be at least 65% to an SUV less than 2.5 (73). On the other hand, Jager found that a decrease of greater than 25% at one week predicted response and changed very little at two months (74). In addition, a good metabolic response predicts a significantly longer time to progression (71,73,74). In contrast, it has been suggested that in a previously treated patient, low FDG avidity in newly recurrent GIST may predict a poor response to tyrosine kinase inhibitor therapy (76).

While RECIST criteria on CT are the standard with the usual decrease in size used as criteria, others have suggested that only a 10% decrease in size as well as a greater than 15% decrease in CT density represents a response to therapy (71,73). These criteria were developed from patients who had FDG PET responses to therapy. Interestingly, CT predicts progression in existing lesions earlier than FDG PET does (70).

SMALL BOWEL

Normal Anatomy of Small Bowel

Mildly increased FDG activity, less than that in the liver, is often seen in the small bowel, secondary to accumulation of the radiotracer in the smooth muscle, and less often as a result of metabolically active mucosa or swallowed

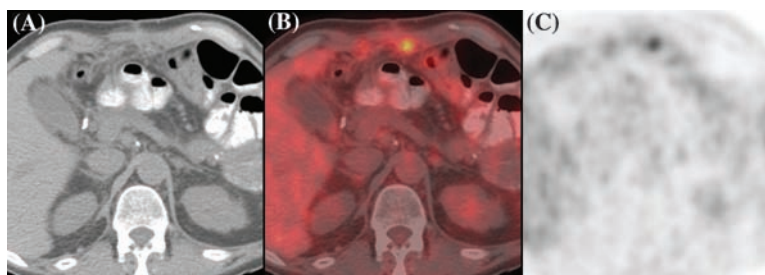


Figure 14 A 43-year-old man with a history of a resected c-kit negative GIST. Noncontrast CT (A) performed as part of the PET/CT shows post surgical changes but is unrevealing in terms of recurrence. The corresponding fusion image (B) and FDG PET (C) shows the focus of uptake at the anterior abdominal wall, which at surgery proved to be recurrent GIST. *Abbreviations:* GIST, gastrointestinal stromal tumor; PET/CT, positron emission tomography/computed tomography.

Table 7 Assessing Response of GIST Tumors to Tyrosine Kinase Inhibitor Therapy, PET Compared with CT

Time point after therapy (reference)	PET criteria (decrease in SUV from baseline)
2 mo (70)	>25%
1 wk (74)	>25%
1 wk (75)	>43%
2 mo (73)	>70% decrease in SUV to <2.5

Abbreviation: SUV, standardized uptake value.

secretions (77). If the involved segment of small bowel is very short, it may appear focal in nature. Correlation with the CT images should demonstrate the portion of intestine with increased metabolic activity. More intense activity may be identified in the gastroduodenal junction or in the ileocecal valve, both likely physiologic due to increased muscle activity in these regions. Again, confirmation of the absence of anatomic abnormality on the CT scan lends greater confidence in the benign nature of this uptake.

Small bowel begins with the duodenum discussed above and may be further divided into the jejunum, which begins at the ligament of Treitz, and the ileum. The border between the jejunum and ileum is arbitrary. The ileum terminates at the ileocecal valve. Jejunal mucosa has a feathery appearance and more prominent folds or valvulae conniventes. The lumen may be wider and the wall appears thicker than the ileum. Ileal folds are less prominent. Normal small-bowel caliber is less than 3 cm and the wall thickness less than 4 mm. The ileocecal valve contains fat and tends to be low in attenuation depending on the amount of fat present. Lipomatous hypertrophy of the ileocecal valve may be seen and should not to be confused with a mass.

The duodenum-jejunal junction should cross midline. Jejunum is normally located predominately in the left abdomen. If not, there may be malrotation of the bowel,

which can range from nonrotation or incomplete rotation of the small bowel around the superior mesenteric artery. Inversion of the normal relation of the superior mesenteric artery (SMA) and superior mesenteric vein (SMV) may be present. Normally SMA should be to the left of the SMV; with malrotation this relationship may be reverse, or they may assume a vertical relationship (78). This finding is helpful for diagnosis but nonspecific, as it may also be seen with normal rotation, volvulus, and occasionally following bowel surgery. The pancreas may also demonstrate morphologic variation such as absence of the uncinate process.

Malrotation may be associated with heterotaxia, asplenia, polysplenia, or IVC anomalies. It may be a complication by obstruction due to midgut volvulus or peritoneal (Ladd's) bands that extend from the cecum to the ligament of Treitz.

Patterns of Disease in the Small and Large Bowel

CT appearance of the bowel wall greatly depends on luminal distention of the bowel. The patterns of wall thickening, the extent of the thickening, and attenuation in the wall of the bowel on CT can be helpful for determining the underlying etiology. In addition, attenuation of the bowel wall is dependent on the administration of IV contrast (79).

Wall Density/ Enhancement Patterns

Homogenous attenuation in a circumferentially thickened bowel loop may be related to submucosal hemorrhage, ischemia and infarction, lymphoma or Crohn's disease (Fig. 15). Mural stratification with alternating layers of high and low attenuation and a "target sign" may also be seen with inflammatory bowel disease and ischemia. Very rarely, a scirrhous type tumor can demonstrate a similar benign appearance. Submucosal fat deposition can be seen in the large or small bowel and is associated with chronic



Figure 15 Cross-sectional view of the terminal ileum (A) demonstrates mural stratification or a “target” appearance with luminal narrowing typical of Crohn’s disease. Contrast-enhanced CT reveals bowel wall thickening localized to the terminal ileum (B) and associated phlegmons. *Abbreviation:* CT, computed tomography.

inflammation. More typically, this is seen in ulcerative colitis (UC) and to a lesser extent Crohn’s disease. Pneumatosis may also demonstrate this stratified pattern as is discussed above. Heterogenous attenuation refers to a mixed pattern of enhancement usually associated with irregular wall thickening and nodularity seen in the setting of neoplasm (Table 8).

Wall Thickening

Mild thickening is usually associated with benign inflammatory or infectious conditions. Marked thickening is typical of severe infection; the most dramatic example is pseudomembranous colitis related to *Clostridium difficile* infection with a thumbprinting or accordion sign pattern related to barium trapped between edematous haustral folds. Symmetric wall thickening favors benign conditions, while more focal, asymmetric, and mass-like thickening favors neoplasm. Thickening of the small-bowel folds with

preservation of the mucosa, i.e., the “picket fence” or “stack of coins” appearance seen on fluoroscopic small-bowel enterography may be seen in vasculitis, hemorrhage, or ischemia. The appearance is related to submucosal edema with preservation of the normal mucosa unlike Crohn’s disease where there is mucosal involvement, for example. Long segments may be involved.

Length of Involvement

Focal processes are typically neoplastic; however, focal inflammation or infection may occur such as diverticulitis, epiploic appendagitis, or appendicitis. Short segments favor benign inflammatory or infectious disease, including radiation enteritis and ischemia. Diffuse involvement may relate to infection, hypoproteinemia seen in the setting of portal hypertension, angioneurotic edema, or vasculitis.

Non-neoplastic Small-Bowel Diseases

Benign Disease

Polyps may occur throughout the GI tract and can range from hyperplastic polyps, a common benign neoplasm, to adenomatous and villous polyps, which are considered premalignant lesions. Polyposis syndromes lead to formation of multiple polyps varying in location depending on the syndrome, and can lead to increased risk of GI and other malignancies.

Pneumatosis intestinalis is seen anywhere along the GI tract and is most worrisome for bowel necrosis and associated with poor prognosis. However, pneumatosis or air within the bowel wall is seen also as a nonemergent finding related to nonischemic conditions ranging from lung diseases, iatrogenic causes such as biopsy or intubation, trauma, infection, inflammatory condition, and collagen vascular disease. Other etiologies include chemotherapy, radiation therapy, and AIDS (80). Gas within the wall of the bowel should not be confused with gas trapped between the bowel wall and intraluminal contents such as a fluid or fecal material.

Inflammatory Bowel Disease

Crohn’s disease is an idiopathic inflammatory disease that can involve any part of the GI tract with the small bowel, specifically the terminal ileum, most commonly affected. Skip lesions with abnormal bowel segments alternating with normal segments, and transmural involvement are findings that distinguish Crohn’s disease from ulcerative colitis. Imaging findings may vary depending on disease activity and chronicity and may include one or more of the following: segmental luminal narrowing including the “string sign” or severe narrowing of the terminal ileum, mural thickening, superficial, and deep ulceration particularly

Table 8 Patterns of Attenuation in the Small Bowel

Pattern of attenuation	Etiology
Homogeneous	Submucosal hemorrhage
	Ischemia and infarction
	Lymphoma
	Crohn’s disease
Mural stratification and “target sign”	Inflammatory bowel disease
	Ischemia
	Scirrhou s type tumor
	Pneumatosis

along the mesenteric border, cobblestoning, or inflammatory nodules separated by linear ulcers, perienteric fat stranding, mucosal hyperenhancement, vascular engorgement or “comb sign,” mural stratification, inflammatory polyps, and fibrofatty proliferation or “creeping fat” (81). Mural thickening >2 mm is considered indicative of small-bowel involvement (82). Complications include strictures, sinus tracts, fistula, abscesses and phlegmon, obstruction, and even carcinoma. On FDG PET/CT performed with water as oral contrast, both SUV and mural thickening have shown excellent correlation with indicators of disease activity including the Crohn’s disease endoscopy index of severity, C-reactive protein levels, and the Crohn’s disease activity index (82). Considering bowel segments that show either increased uptake of FDG and/or wall thickening, sensitivity of PET/CT compared with endoscopy was about 73% with a specificity of 55%, but if both criteria were evident, the sensitivity fell to 54% but specificity increased to 72% (82). Sensitivity for severe and moderate-to-severe lesions was very high, however. In another smaller series of patients, using qualitative bowel uptake with liver uptake comparisons on PET/CT, moderate- to markedly-increased uptake had a high correlation with endoscopically detected inflammation in Crohn’s disease (83). In a small series of children, FDG PET alone had a 100% sensitivity, 86% specificity, and 90% accuracy for detecting small-bowel activity (83). In a series of 51 patients where SUV was used to assess disease activity, PET had an 85% sensitivity for disease in the terminal ileum and colon, higher than either MRI or radiolabeled granulocytes and a comparable specificity (89%) (84). In that series the average SUV for inflamed bowel was 4.4.

Diverticular Disease

Small-bowel diverticula may be congenital or acquired. Congenital diverticula are true diverticula and involve all three layers of the bowel wall forming along the anti-mesenteric border. When they occur in the ileum within three feet of the ileocecal valve, they are known as Meckel’s diverticulum and may contain heterotopic mucosa, usually gastric mucosa (85). Acquired diverticula are more commonly found in the jejunum along the mesenteric border because of weakness in the bowel wall. Both appear as focal outpouchings of the bowel wall and may contain air and fluid or debris. Diverticulitis of the small bowel is rare but can occur in the duodenum, jejunum, and ileum. Small-bowel diverticulitis may present as an inflammatory mass, segmental wall thickening with fat stranding, and may cause obstruction or perforate with abscess formation (86). Differential diagnosis includes perforated neoplasm, foreign body, Crohn’s disease, and ulceration due to nonsteroidal anti-inflammatory

drug use (87). Diverticulitis of the small bowel has not been described on PET, but in the large bowel is FDG avid.

Bowel Obstruction

Bowel obstruction is most commonly caused by adhesions, hernia, or neoplasm, but other causes such as appendicitis, inflammatory bowel disease, foreign bodies, endometriosis, and gallstones should be considered. CT may be used, as opposed to ileus, to confirm obstruction, determine the point of transition, and determine the underlying cause, but also can assess the severity of obstruction and identify complications such as ischemia or perforation. Obstruction is likely if there is bowel dilatation and air-fluid levels with distal bowel collapse. The degree of dilation, and relative distal bowel collapse depends on the severity and duration of the obstruction (Fig. 16). The point of obstruction or the transition zone may be identified by finding the point at which there is an abrupt change in the caliber of bowel loops. “Small-bowel feces” sign is also helpful where material within the bowel, similar in appearance to fecal material, accumulates at the point of obstruction (88). Ischemia can develop, particularly in closed loop obstructions. Signs of ischemia include wall enhancement, ascites, engorgement of mesenteric veins, and wall edema (89).

Intussusception of the small bowel may occur and cause obstruction (Fig. 17). Transient intussusceptions, which resolve spontaneously, may occur and are of no clinical significance. More concerning are intussusceptions



Figure 16 Another patient presented with small-bowel obstruction secondary to a newly discovered colon carcinoma. (A–B) shows dilated small-bowel loops with air-fluid levels.

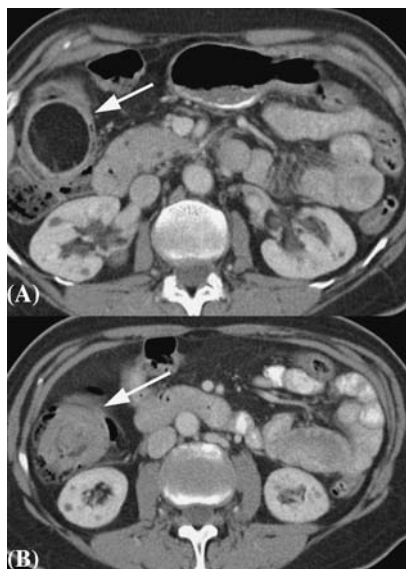


Figure 17 (A) Axial contrast-enhanced CT shows a benign mass, a lipoma (*arrow*) without any evidence of bowel obstruction. However, there is an ileocolic intussusception (*arrow*) caused by the lipoma (B). *Abbreviation:* CT, computed tomography.

caused by discrete masses that may intermittently lead to obstruction.

Infectious Enteritis

Infectious enteritis may be due to bacterial, viral, or parasitic pathogens. CT findings may be nonspecific unless parasites are visualized with the bowel lumen. Tuberculosis (TB) most commonly involves the ileocecal region where FDG PET uptake has been reported in association with ileocecal involvement (90). PET activity has also been localized to jejunal wall thickening on CT secondary to TB (91). Whipple disease caused by a gram-positive bacillus may lead to nodular fold thickening of the small-bowel folds associated with bulky low attenuation lymphadenopathy. *Mycobacterium avium* intracellulare infection typically seen in immunocompromised patients may appear similar to Whipple disease. The extensive lymphadenopathy may make it difficult to distinguish from lymphoma. *Yersinia*, *Campylobacter*, or *Salmonella* usually causes infectious terminal ileitis. Circumferential wall thickening may be seen with involvement of the cecum and associated lymphadenopathy (92).

Vascular Disorders

Submucosal hemorrhage is seen in patients on anticoagulation therapy, or in the setting of trauma or an underlying bleeding diathesis. Typical findings include symmetric circumferential wall thickening with homogenous high attenuation and lack of enhancement.

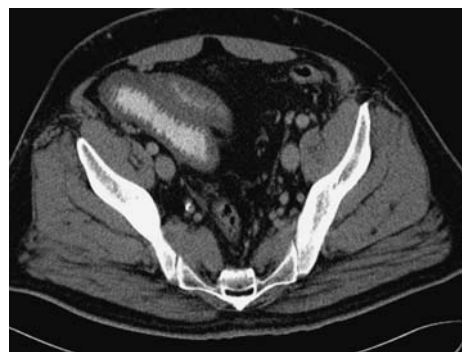


Figure 18 CT performed in a patient with hepatocellular carcinoma and acute pain with abnormal small-bowel loops demonstrating thick parallel folds giving a “stacked coin” or “picket fence” pattern. This pattern is typically due to submucosal deposition of edema or blood, which can be caused by intramural hemorrhage, ischemia, vasculitis, angioedema, and hypoalbuminemia. In this case, there was superior mesenteric vein thrombosis and resulting venous ischemia. *Abbreviation:* CT, computed tomography.

In the setting of ischemia (Fig. 18) there may be circumferential thickening, mucosal enhancement, and submucosal low attenuation due to edema with serosal enhancement yielding a “target sign” or mural stratification pattern. This pattern is more typical of a benign process, rather than a neoplastic one. With infarction, there may be no mural thickening or wall enhancement.

Diffuse Enteropathies

Adult Celiac Disease or sprue due to hypersensitivity to gluten leads to an increased incidence of non-Hodgkin’s lymphoma, esophageal, duodenal, and rectal carcinoma. CT findings include bowel dilatation and fluid excess, jejunoileal fold pattern reversal, small-bowel intussusception, and mesenteric lymphadenopathy (93). FDG PET may be occasionally positive in refractory celiac disease but has been found to be highly sensitive and specific in detecting the conversion to enteropathy associated T-cell lymphoma, which may develop in patients with this disease (94).

Scleroderma may lead to luminal dilatation with apparent thinning of the folds or valvulae conniventes due to collagen deposition in the underlying bowel wall muscle. Contraction due to fibrosis along the mesenteric border may lead to pseudosacculations along the antimesenteric border. The duodenum and jejunum are more often affected.

Radiation enteritis may be seen in the acute or chronic setting and more commonly affects the distal small bowel. Acutely, radiation may cause mural thickening and submucosal edema, later progressing to effacement of normal bowel-wall fold pattern, ulceration, and stricture due to fibrosis. Adhesions, as well as sinus tracts and fistula, may develop.

Graft versus Host disease is a life-threatening complication of bone marrow transplantation and may affect the skin, liver, and GI tract. Small-bowel fold thickening, effacement of folds, luminal narrowing, engorgement of the vasa recta, and ulcerations may be present (95,96).

Benign Tumors and Related Findings in the Small Bowel

Benign tumors with a differential diagnosis similar to that of the esophagus and stomach may be seen. It may be difficult to distinguish between benign and malignant on CT, although benign lesions tend to be smaller and well circumscribed. Lipomas are easily identified as distinct entities as they are well circumscribed, fat-density masses most frequently seen in the colon and small bowel (Fig. 17). Lipomas like adenomas and leiomyomas are in general not FDG avid, and are likely indistinguishable from the background physiologic uptake in the bowel. In fact, in one study, the authors suggest that an SUV cut off of 2.7 was useful in distinguishing an adenoma from malignancy (97). Surgical procedures in the small bowel usually involve a primary end-to-end anastomosis with high-density suture or staples at the anastomotic site. These can occasionally cause beam-hardening artifact on attenuation corrected PET images.

Small-Bowel Malignancy

Small-bowel neoplasms typically present as eccentric, asymmetric wall thickening that can be focal or segmental (Fig. 19). A mass may be present which can range from a smooth to lobulated to irregular in morphology. A wall thickness of greater than 5 mm is considered abnormal and tumors usually present with thickening greater than 15 mm. Tumor may be homogenous or heterogenous depending on size and vascularity. The most common pitfall in imaging is incomplete distention or inadequate luminal contrast opacification. While dilute barium may be used to achieve this, work has also been done with negative oral contrast medium to visualize the small bowel (5).

Adenocarcinoma

Adenocarcinoma is most commonly found in the duodenum and jejunum. Duodenal adenocarcinomas may be difficult to differentiate from pancreatic or ampullary carcinomas. These tumors present as eccentric focal masses, irregular wall thickening with associated annular constriction or ulcerated lesions, and will be FDG avid (Fig. 19) (98,99). They tend to spread to regional lymph nodes and invade the root of the mesentery (100).

Carcinoid

Carcinoid tumors may occur in the GI tract and pancreas but most commonly arise in the ileum. They tend to be hypervascular masses and may be multicentric. The primary carcinoid may not be seen but the tumors grow into the mesentery and more commonly present as a spiculated or stellate mesenteric soft tissue mass with calcification (Fig. 19) (96,101,102). Hypervascular liver metastases may be seen. Other neuroendocrine tumors may be considered in the differential, but more commonly occur in the duodenum. Carcinoid of the small bowel is variable in FDG avidity (103–106), but other radiopharmaceuticals including ^{11}C -labeled serotonin precursor 5-HTP (107,108), positron-labeled somatostatin receptor ligands used in either PET/CT or coregistered PET/MRI (109,110), and L-DOPA PET (111–113) are showing promising signs of future use in PET imaging of these tumors (114). On occasion, FDG may be useful in delineating the other endocrine neoplasias that may be coincident with carcinoid (103).

Lymphoma

The small bowel is the second most common location for lymphoma in the gastrointestinal tract after the stomach, with the distal ileum the most common site in the small bowel (115). Lymphoma, more thoroughly discussed in chapter 17, presents as circumferential wall thickening with a relatively homogenous appearance, but can ulcerate. There is usually an associated luminal dilatation, rather than a narrowing, making obstruction rare. Also, lymphoma tends to involve a longer segment of bowel compared with other small-bowel neoplasms. Rarely, lymphomas can lead to intussusception. On FDG PET, uptake may be diffuse or multifocal uptake arrayed along the loop of small bowel (116). As mentioned above, in enteropathy related T-cell lymphoma, FDG PET tends to show a fairly elevated SUV (117) and has been shown to be sensitive (100%) and specific (90%) compared with 53% specificity for CT with comparable sensitivity (94).

More importantly, FDG PET has tremendous value in evaluating response to therapy for lymphoma. In a series of 19 patients with non-Hodgkin's lymphoma of the gastrointestinal tract, 15 of whom had small-bowel involvement, PET showed a 95% accuracy compared with 79% for CT in predicting response to therapy (118). While a negative PET was no different in terms of predicting disease-free survival compared with a negative CT, a positive PET portended a significantly poorer disease-free survival than a positive CT did (118).

Metastases

Metastases may spread via direct extension from adjacent organs such as the pancreas and colon by intraperitoneal

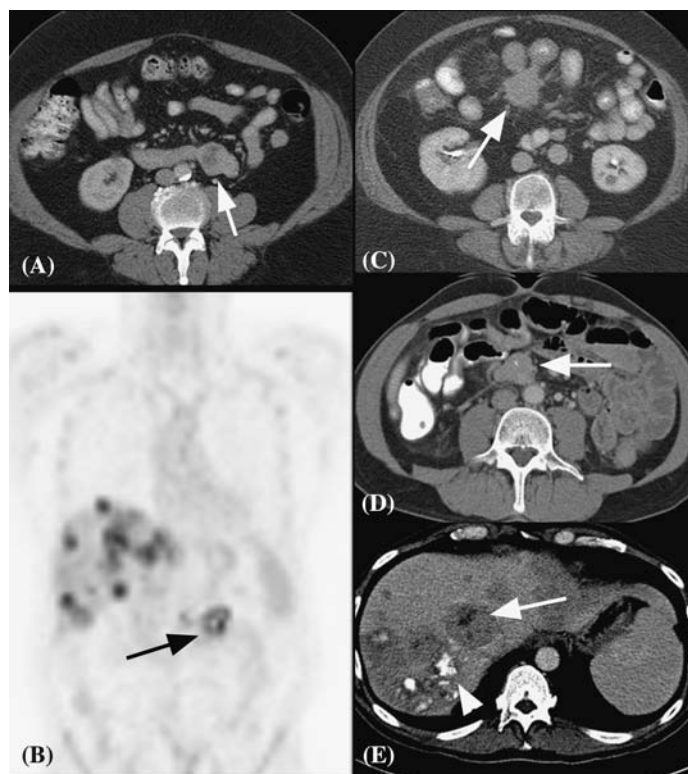


Figure 19 (A) Contrast-enhanced CT in a patient with newly diagnosed GIST of the small bowel shows (*white arrow*) a mass in the duodenum. (B) Coronal FDG PET shows uptake in a primary adenocarcinoma of the small bowel (*arrow*) with multiple foci of uptake in the liver compatible with metastases at the time of presentation. (C) Axial contrast-enhanced CT scan in another patient demonstrates a mesenteric mass (*arrow*) compatible with a carcinoid tumor with associated spiculation in the mesentery. (D) Axial contrast-enhanced CT scan in still another patient, with recurrent carcinoid tumor demonstrating calcification (*arrow*) and (E) metastases. Previously treated metastatic liver lesions demonstrate calcification (*arrowhead*) while the new untreated metastases lack calcification (*arrow*). *Abbreviations:* PET, positron emission tomography; CT, computed tomography; GIST, gastrointestinal stromal tumor.

seeding as in ovarian cancer or hematogenously from lung, breast cancer, melanoma, and renal cell carcinoma. Melanoma usually presents with multiple extrinsic masses but can present as polypoid masses with central ulceration giving a target appearance and may lead to transient intussusception and perforation (102). As with most melanoma, PET is useful in identifying unsuspected small-bowel metastases (119).

COLON

Normal Anatomy of Colon

The colon may be divided into segments including cecum, appendix, ascending colon, splenic flexure, transverse, hepatic flexure, descending, sigmoid, rectum, and anal canal. The appendix is usually located in the right lower quadrant, 3 cm below the ileocecal valve and can be quite variable in length. It is a blind ending tubular structure

typically less than 6 mm in diameter which should fill freely with gas or contrast material. The colon is identified by the normal haustrations, which are slight infoldings of the wall. The cecum is a blind pouch below the ileocecal valve. The cecum is usually located in the right-lower quadrant but can be mobile. The sigmoid is also very mobile and may be redundant. The rectum begins at approximately the level of S2–S4. The anal canal is surrounded by the levator musculature and is approximately 3–4 cm in length. Malrotation may also involve the colon to varying degrees. Physiologic distribution of radiopharmaceutical in the colon can range from minimal, barely discernible from the background, to extensive and diffuse, and is a function of smooth muscle uptake as well as swallowed secretions or excretion and accumulation of FDG within the contents of the colon (77). While diffuse FDG PET uptake in the colon may be normal, segmental uptake is suggestive of inflammatory disease and focal uptake can be either inflammatory or neoplastic (Fig. 20) (120).

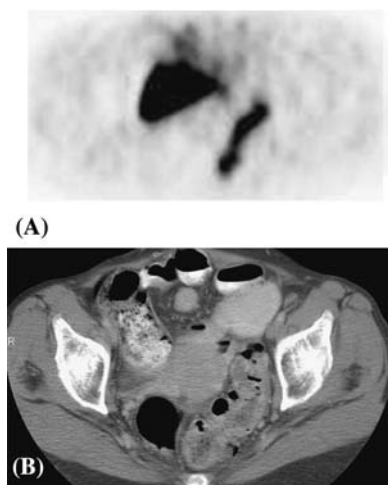


Figure 20 A 63-year-old with metastatic disease underwent a PET and a diagnostic CT. FDG PET (A) showed segmental bowel uptake. A contrast-enhanced CT (B) performed a day earlier shows subtle thickening of a segment of sigmoid colon corresponding to the bowel uptake on PET. The patient also had a history of Crohn's disease, which was mildly active at the time although the patient was without significant complaints. *Abbreviations:* PET, positron emission tomography; CT, computed tomography.

Non-neoplastic Diseases of the Colon

Infection

Typhlitis or neutropenic colitis is seen in immunocompromised patients usually undergoing chemotherapy. Typically, it affects the cecum and terminal ileum and results from loss of the host defenses to intestinal organisms. CT findings are nonspecific but include marked circumferential cecal wall thickening with pericecal fat stranding, and can progress to ischemia (121). Location of disease and clinical history is most helpful for diagnosis. Differential diagnosis includes inflammatory bowel disease, infection, ischemia, and appendicitis. While PET findings are also nonspecific, intense uptake fusing to large-bowel wall should suggest neutropenic colitis in postchemotherapy patients (Fig. 21) (122). PET has been valuable in detecting unsuspected but clinically threatening infections of the large bowel in this setting (122).

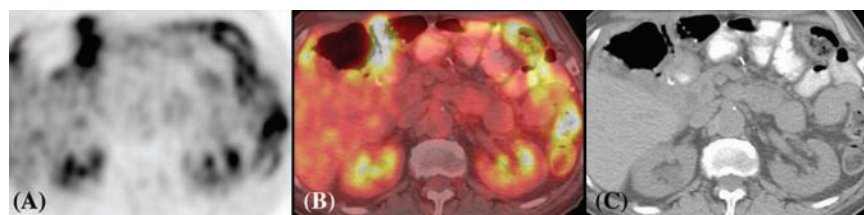


Figure 21 A 72-year-old man on chemotherapy for gastric adenocarcinoma complaining of abdominal pain and diarrhea. FDG PET from a PET/CT (A) shows abundant metabolic activity fusing (B) to the wall of the colon on the corresponding CT slice (C). On CT, there is no significant thickening in the left colon despite the obvious uptake on the FDG PET suggesting the presence of a pancolitis. *Abbreviations:* PET, positron emission tomography; CT, computed tomography.

Pseudomembranous colitis is an acute infectious colitis associated with use of antibiotics, which alter the normal colonic flora setting the stage for bacterial overgrowth of *Clostridium difficile* most commonly. This organism releases enterotoxins leading to mucosal inflammation. FDG PET uptake has been reported in association with pseudomembranous colitis (123). CT findings may vary from mild inflammation to more classic findings, including marked wall thickening and "thumbprinting" due to low attenuation in the colic wall related to marked edema. The accordion sign is also helpful because of trapping of positive or bright contrast material between thickened haustral folds (124). A target sign and ascites may also be present. Complications include toxic megacolon and perforation. The entire colon is typically involved, but it may present with segmental involvement and may be confused with Crohn's disease.

CT findings in infectious colitis show considerable overlap, so that clinical history, stool samples, colonoscopy, and/or biopsy are required. Most infectious colitides involve the entire colon, such as *cytomegalovirus* and *E. Coli*, but some are limited to the right colon, such as salmonella, *Yersinia*, TB, and amebiasis. Others are more left-sided, such as schistosomiasis, shigella, and herpes. Isolated reports of PET detection of infectious colitis in both children and adults suggest that FDG PET may be as sensitive or more than radiolabeled white blood cells, and can be particularly useful in patients without localizing symptoms (125,126).

TB of the bowel most commonly occurs in the ileocecal region and the majority of patients have no evidence of active or chronic TB on chest radiography (121). It can mimic Crohn's disease as findings include wall thickening of the ileum and cecum with cecal scarring, lymphadenopathy, which may demonstrate central low attenuation or may contain calcification, strictures, rarely fistula, and sinus tracts (121,124).

Inflammatory Bowel Disease

Ulcerative colitis (UC) vs Crohn's disease

UC classically involves the rectum more so than in Crohn's disease with contiguous involvement of the

Table 9 Ulcerative Colitis vs. Crohn's Disease

Ulcerative colitis	Crohn's disease
Rectal involvement more likely	Rectal involvement less likely
Contiguous involvement	Discontinuous involvement, skip lesions with deep, transverse and longitudinal ulcers with intervening edema (cobblestone appearance of the mucosa)
Mucosal	Transmural involvement leads to greater degrees of wall thickening
Involves the colon primarily but backwash ileitis may occur	May occur any where along the GI tract but terminal ileal involvement common and may lead to structuring (string sign)
No fistulae, abscesses, phlegmon	Fissures, sinus tracts, fistulae, abscesses, phlegmon
Lead pipe appearance in advanced disease Risk of toxic megacolon	Fibrofatty proliferation in the mesentery (creeping fat)
Associated with primacy sclerosing cholangitis	Engorgement of mesenteric vascular bundles (comb sign)
	Additional extraintestinal findings renal and gallbladder calculi, sacroileitis, hepatic steatosis, pancreatitis

colon as opposed to skip lesions seen in Crohn's disease (Table 9). The left-sided colon or the entire colon may be involved and is rarely seen isolated to the right colon. It is a mucosal process unlike Crohn's disease, which is transmural (Fig. 20). Wall thickening, a target sign, and submucosal fat deposition may be seen. In advanced disease the colon loses its normal haustral folds and becomes featureless with a "lead pipe" appearance. Although "backwash" ileitis may occur, the terminal ileum is not usually involved in UC. Perirectal fat hypertrophy can be seen. Lymph nodes are not typically enlarged. Fistulae, abscesses, or phlegmon are seen in Crohn's disease, and not in UC. Complications of UC include toxic megacolon, sclerosing cholangitis, and sacroileitis. MRI is helpful for delineation of perirectal fistulae and abscesses, which may result as a complication of Crohn's disease.

Toxic megacolon is a serious potential complication of many of the colitides and is manifested by marked diffuse colonic dilatation with air-fluid levels with an irregular mucosal pattern and loss of normal haustration in the setting of systemic sepsis (124,127).

Diverticulitis and appendicitis

Diverticulosis of the colon is acquired outpouchings of the colonic wall usually containing air or contrast material. Diverticulosis can be seen throughout the colon sparing the rectum and anus. They are more typically left sided but can occur on the right side and mimic appendicitis, among other disease processes. These occur along the mesenteric sides and are thought to be related to increased intraluminal pressure. Diverticulitis is a result of microperforation of these outpouchings usually secondary to obstruction from food of fecal material. Muscular hypertrophy secondary to chronic inflammation may occur and result in circumferential wall thickening that can mimic neoplasm. CT imaging features of diverticulitis include pericolic fat stranding sometimes isolated to the peridiverticular region but possibly more extensive, bowel wall thickening, which may be asymmetric and isolated to

the peridiverticular regions, small air bubbles, air/fluid collections, abscesses, and phlegmon (Fig. 22) (Table 10) (124,127). Adjacent inflammatory changes may be present in the small bowel, which can confound diagnosis. Occasionally, a sinus tract or fistula to adjacent organs may occur, sometimes presenting as abnormal collections of gas in the bladder or uterus in a patient with no history of catheterization of other intervention. Giant diverticulae may be seen as a result of prior inflammation or abscess formation and if filled with air and fluid, they may mimic abscesses or bowel obstruction, but lack pericolic inflammatory changes or clinical symptoms. Diverticulitis has been seen to cause FDG uptake (122,128) and may appear focal, localizing to the diverticulum, or more segmental when there is a more significant disease (Fig. 22).

Appendicitis presents with abdominal pain, classically a periumbilical pain radiating to the right lower quadrant; but depending on the position of the appendix, symptoms may vary. Clinical history and laboratory data are important to aid in diagnosis. On CT, the appendix may become enlarged with a diameter greater than 6 mm as a result of obstruction; a hyperdense calcification or appendicolith may be present (Table 11). Contrast will be unable to opacify an obstructed appendix (Fig. 23). Wall enhancement, thickening, periappendiceal fat stranding, ascites, secondary cecal changes with eccentric wall thickening near the appendiceal orifice, or inflammation in adjacent structures such as the terminal ileum, may be present (129). Occasionally, only the tip may be inflamed. Perforation may occur such that extraluminal gas, air/fluid collections, abscesses, and phlegmon may develop with associated lymphadenopathy. In neutropenic patients, appendicitis may be asymptomatic (130) and in this setting the incidental identification of appendicitis by FDG PET may be of value.

Mucocoele of the appendix

Mucocoeles occur secondary to chronic appendiceal obstruction and are usually found incidentally. They are asymptomatic

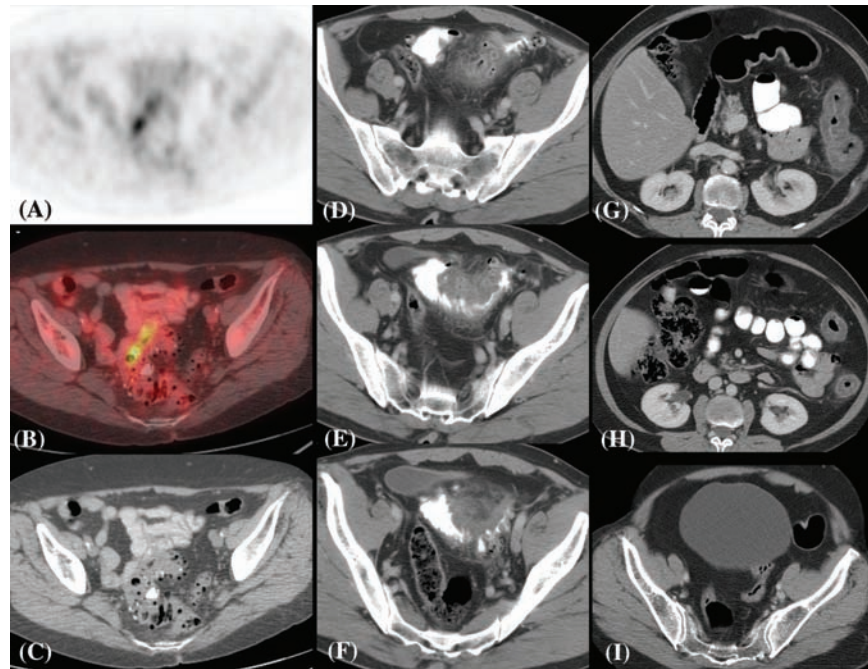


Figure 22 (A–C) A 54-year-old woman with lung cancer. (A) FDG PET from a PET/CT shows uptake in the pelvis fusing (B) to a segment of colon that shows diverticulosis. Further history revealed a week of intermittent lower abdominal pain. Another patient has more flagrant CT findings of diverticulitis (D–F) with eccentric colonic wall thickening around diverticuli and pericolonic fat stranding. The asymmetric wall thickening can be seen with malignancy such that follow-up may be warranted. Follow-up in this patient revealed complete resolution of findings. CT (G–H) of another patient with ischemic colitis shows a segment of colon at the level of the splenic flexure with a thickened bowel wall and mucosal enhancement. The location and short segment of involvement is typical of ischemia affecting a watershed area where collateral supply is limited, leading to vulnerability to the colon to ischemia in the setting of low flow states. Note the sparing of the sigmoid colon (I). *Abbreviation:* PET/CT, positron emission tomography/computed tomography.

Table 10 CT Features of Diverticulitis

Pericolonic fat stranding
Bowel wall thickening
Air bubbles
Air/fluid collections
Abscesses
Phlegmon
Inflammatory changes in adjacent small bowel
Sinus tract
Fistulae with air in bladder or uterus

Table 11 CT Findings of Appendicitis

Diameter of appendix >6 mm
Calcified appendicolith
Unopacified by oral contrast
IV contrast enhancement of wall
Wall thickening
Periappendiceal fat stranding
Ascites
Eccentric wall thickening of the cecum or terminal ileum
Perforation with extraluminal gas or abscess

unless they become infected. The appendix becomes distended with fluid density material manifested by a fluid density blind ending tubular structure arising from the base of the cecum (Fig. 23). Mural calcification may be present but the presence of wall thickening, irregularity, or a soft tissue mass raises concern for malignancy. Pseudomyxoma peritonei results from mucocoele rupture, usually the malignant form, spreading mucin through the peritoneal cavity mimicking ovarian carcinomatosis.

Non-neoplastic Fat Density Lesions

Epiploic Appendagitis

Epiploic appendages are fatty structures, which contain blood vessels and arise from the serosal surface of the colon and are more commonly seen in the sigmoid colon, but may be seen throughout the colon except the rectum. They can become inflamed or ischemic, resulting in abdominal pain. One should be familiar with the distinguishing features of this entity to differentiate it from diverticulitis, appendicitis, tumor, or omental infarct. Normally these appendages are not seen on CT unless there is

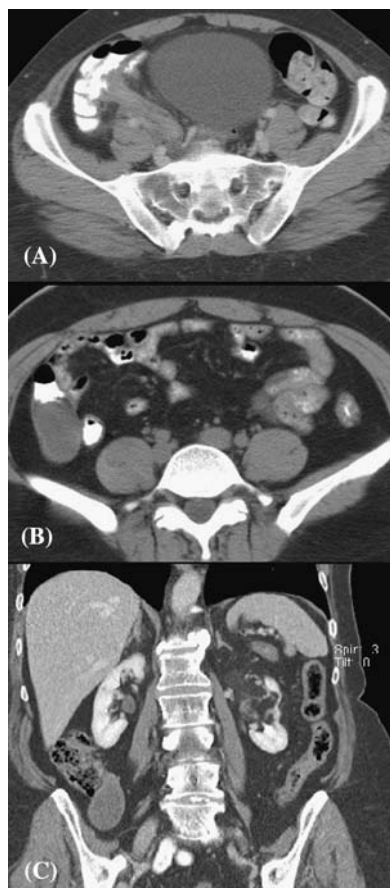


Figure 23 Axial contrast-enhanced CT (A) demonstrates a nonfilling appendix despite contrast in the cecum with edema at the appendiceal orifice, appendiceal wall thickening, luminal distention, and periappendiceal fat stranding compatible with acute appendicitis. Fluid-filled structure in the expected region of the appendix (B, C) on axial and coronal reformatted contrast-enhanced CT with a slightly thickening wall compatible with a mucocele of the appendix due to chronic obstruction of the appendix. *Abbreviation:* CT, computed tomography.

ascites fluid surrounding it or there is inflammation. Epiploic appendagitis is a self-limiting process and no intervention is required, just conservative management. Findings include an ovoid fat density structure adjacent to the colon surrounded by inflammatory changes (Fig. 24). There may be a central dot or high attenuation focus likely representing a thrombosed vein (131). There may be pericolonic fat stranding but usually in the absence of wall thickening.

Omental Infarct

Other benign disease processes involving the abdominal fat that need to be considered are omental infarcts, which

may look similar to epiploic appendagitis, but present more as omental mass with haziness or increased density in the fat with surrounding inflammatory changes. These tend to occur centrally or in the right lower quadrant; epiploic appendagitis will occur more often adjacent to the sigmoid colon (Fig. 24).

Sclerosing Mesenteritis

Sclerosing mesenteritis is another inflammatory process within the abdominal fat, specifically the small-bowel mesenteric fat, but can involve the mesocolic, omentum, peripancreatic region, and retroperitoneum. On CT, it presents as a hazy region of increased density (Fig. 24) and may be associated with lymphadenopathy mimicking the appearance of lymphoma. There are different presentations of this process depending on the predominant component. Mesenteric panniculitis is manifested by chronic inflammation, mesenteric lipodystrophy by fat necrosis, and retractile mesenteritis by fibrosis, which can mimic tumors such as desmoid or carcinoid tumors (96,131). It is a self-limiting process that can cause abdominal pain. On PET/CT, this area of uptake will be metabolically active, but unlike lymphomatous involvement, the activity will not resolve with treatment (132,133).

Ischemia

Ischemia is usually caused by low-flow secondary to shock, myocardial infarction, arrhythmia, emboli, thrombosis, or trauma. Other etiologies include obstruction due to a neoplasm, volvulus, fecal impaction (stercoral colitis), incarcerated hernia, or diverticulitis (134). Colonoscopy is most useful for diagnosis. Some segments of the colon are more susceptible to ischemia depending on the amount of collateral flow present. Most commonly, ischemia affects the watershed areas that include the transverse colon near the splenic flexure in the right-upper quadrant, and the rectosigmoid junction in the left-lower quadrant. Ischemia presents as wall thickening, edema, thumbprinting, pericolonic fat stranding, and ascites (Fig. 22) (Table 12). Reperfusion injury may manifest as high attenuation hemorrhage in the bowel wall or as a pseudomass (124). Infarction leads to development of a thin, nonenhancing wall with distention of the lumen and eventually with pneumatosis, mesenteric venous, and portal venous gas.

Ischemia may occur proximal to an obstructing colon cancer and lead to overstaging of cancer on CT imaging. Ischemic segments demonstrate smooth circumferential wall thickening with homogenous enhancement or a target sign versus cancer, which tend to lead to nodular thickening and heterogeneous enhancement (134).

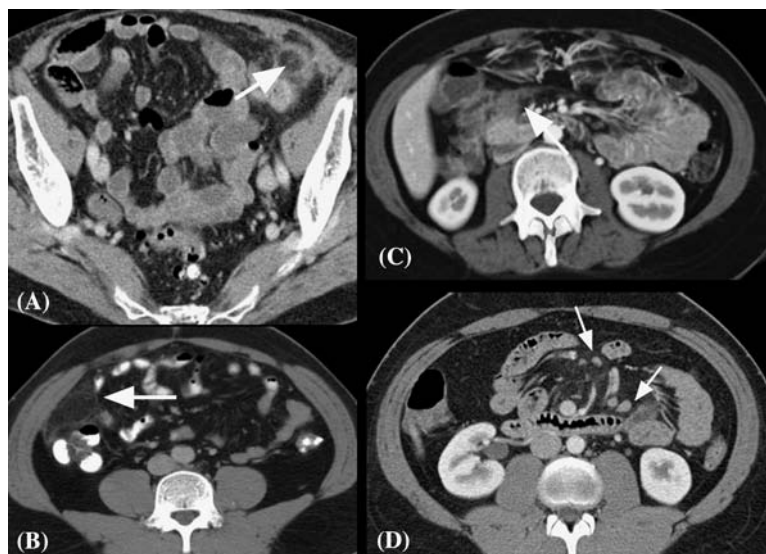


Figure 24 Abdominal pain may be caused by a variety of causes including epiploic appendagitis (A). Note the ovoid fat density structure adjacent to the colon with rim enhancement and surrounding inflammatory changes. The central high attenuation “dot” (arrow) likely represents a thrombosed vein. Note the absence of wall thickening in the adjacent colon. In another patient with right lower quadrant pain, there is focal fat density (B) with a haziness appearance (arrow) compared with normal mesenteric fat represents typical of an omental infarct. Contrast-enhanced CT in another patient with abdominal pain demonstrates a mesenteric soft tissue mass found to be (C) fibrosing mesenteritis (arrow) although differential considerations include carcinoid tumor. Finally, a patient with abdominal pain and (D) multiple, enlarged lymph nodes in the small-bowel mesentery (arrows) suggestive of mesenteric adenitis. *Abbreviation:* CT, computed tomography.

Table 12 Findings of Ischemia of the Colon

Ischemia	Infarct
Circumferential wall thickening	Thinned wall
Submucosal edema	No IV contrast wall enhancement
Thumbprinting	Luminal distention
Pericolonic fat stranding	Pneumatosis
	Pneumoperitoneum
Ascites	Venous and portal gas

Radiation Colitis

Radiation-induced colitis may appear similar to ischemic colitis radiographically but is confined to the site of radiation. This is usually in the midline pelvis causing rectal wall thickening and perirectal fat stranding acutely, with perirectal or intramural fat deposition seen in the chronic stage (124). Postradiation type changes are generally diffuse and nonfocal in nature in contradistinction to viable tumor, which is more focal and more intense. In immediate postradiation treatment inflammation, distinguishing radiation colitis from residual tumor may be a challenge. However, FDG PET can assess residual tumor versus scarring (135) on the basis of the pattern of uptake, as well as the degree of metabolic activity. Delay of

posttherapy PET scan to six or more weeks following radiation increases specificity.

Benign Rectoanal Diseases

CT of the rectum and anus is limited. Virtual CT colonography is more useful but MRI is the modality of choice for assessing perirectal fistula and perirectal masses because of the better contrast resolution. Perirectal fistula and abscesses are most often found in patients with Crohn's disease but can be seen as a result of foreign body perforation, infection, or neoplasm and can be evaluated with MRI. Normal FDG PET uptake in the rectum can be fairly intense.

Hemorrhoids, particularly thrombosed hemorrhoids, can mimic perirectal masses and lymph nodes. Patients with portal hypertension are more likely to present with prominent perirectal varices. Contrast-enhanced imaging in the venous phase is as useful as multiplanar reconstructions to differentiate between masses and serpiginous vascular structures.

Neoplastic Diseases of the Colon

Benign Neoplasms

Lipomas can be easily identified by their fatty composition. Adenomata and polyps are better seen with virtual

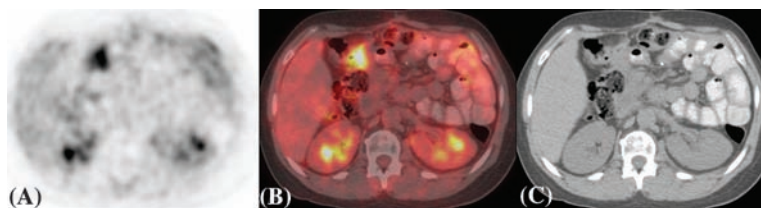


Figure 25 A 56-year-old woman with a history of lymphoma underwent a PET/CT for monitoring of possible recurrence. FDG PET showed a focus of increased uptake in the right upper abdomen (A) that fused (B) to a soft tissue density in the transverse colon on CT (C). Subsequent colonoscopic biopsy revealed adenocarcinoma of the colon. *Abbreviation:* PET/CT, positron emission tomography/computed tomography.

CT colonography because visualization requires adequate luminal distention. Adenomatous polyps are often detected incidentally on whole body images acquired for other indications, with a sensitivity of 24%. The typical lesion size range that may be visualized by PET/CT is 5 to 30 mm. If the lesion is larger than 13 mm, the positivity rate increases to 90% on FDG PET. Although PET is not recommended for detection or screening for precancerous or malignant neoplasms, identification of focal colon uptake requires follow-up and may warrant colonoscopy for further evaluation (Fig. 25) (136).

Colorectal Malignancy

As with any malignancy of the GI tract, CT sensitivity depends on the size of the lesion, whether the bowel is well distended with contrast, and whether IV contrast has been utilized and optimal timing of contrast enhancement is achieved. Again interactive post-processing techniques, such as multiplanar reconstructions and volume rendering, are invaluable tools for assessing the bowel. MRI is particularly useful for staging of rectal malignancies.

The most common primary malignancy is adenocarcinoma. Other neoplasms that less commonly arise in the colon include lymphoma, GIST, carcinoid, squamous carcinoma, melanoma, and colonic metastases. Most common metastases to the colon include lung, breast, and ovarian carcinoma. Carcinoid tumors occur most commonly in the appendix followed by the ileum, lung, and rectum.

Primary adenocarcinoma of the colon

Although FDG PET is sensitive for colon carcinoma, its use as a diagnostic tool is usually confined to detection of recurrence, since the yield of PET when used as a screening tool is relatively low (137). Nonetheless, primary colon carcinomas have not infrequently been detected in studies done for other reasons (137–141). It should be noted that mucinous adenocarcinoma might cause false negative results. The latter is most likely a function of the relative hypocellularity of mucinous tumors as well as the minimal glucose metabolism of mucin.

Typically, colon cancers present on CT as discrete soft tissue masses that cause focal narrowing of the lumen with

an “apple core” appearance caused by focal constriction of the colonic lumen (Fig. 26). Large masses may demonstrate low attenuation and hypovascular regions due to necrosis or

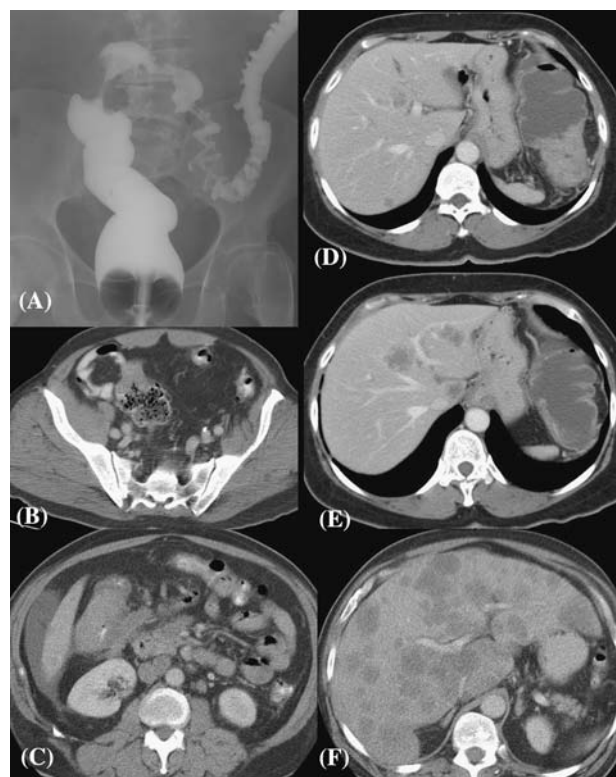


Figure 26 A 72-year-old woman with an apple-core lesion of the sigmoid colon (arrow) seen on barium enema (A) and on axial CT (B). Contrast-enhanced CT in another patient with a colon cancer (C) at the hepatic flexure with aortocaval lymphadenopathy. Yet another patient with a newly diagnosed colon carcinoma who underwent diagnostic CT which shows the lesion in the splenic flexure causing a colonic obstruction (D) with irregular rim enhancing hypoattenuating liver metastases on the portal-venous phase of the contrast study (D–E). The final patient presented with a history of colon-cancer status post resection with rising CEA after a tumor and adjuvant chemotherapy with axial contrast-enhanced CT demonstrating widespread liver metastases (F). *Abbreviations:* CT, computed tomography; CEA, carcinoembryonic antigen.

ulceration. Asymmetric wall thickening with luminal narrowing is another common finding. There may be pericolic fat stranding due to inflammation or tumor infiltration with associated regional lymphadenopathy. Colonic tumors may present with obstruction, intussusception, fistulas, or perforation. Local spread may occur to adjacent organs with loss of normal fat planes. Nodal metastases vary in size and morphology and CT alone, although very sensitive to lymphadenopathy, is not very specific.

Staging of colon cancer

CT and pelvic MRI are standard staging procedures in patients initially diagnosed with colon cancer (142,143). Of the patients diagnosed with primary colon cancer each year, about 20% will present with liver metastases (144) requiring neoadjuvant chemotherapy prior to surgical management (Fig. 27). Like detection of primary tumors, PET/CT has not been much touted for staging of primary cancers. Nonetheless, studies have shown FDG PET to be more sensitive and more accurate, but less specific than CT alone, for staging of primary colon carcinoma (145). The strength of PET, relative to CT, lies in the detection of liver metastases at the time of diagnosis (146). Both modalities perform poorly in staging lymphadenopathy compared with surgery (143,146) for colon cancer although accuracy of CT for lymphadenopathy from rectal cancer is higher (143).

Postoperative changes in the colon

Colonic surgery varies depending on whether the pathologic entity is inflammatory or neoplastic, benign or malignant, and on the location of the lesion. Segmental resection may be performed with end-to-end or end-to-side anastomoses. A colostomy or surgical colocutaneous fistula may be warranted if the bowel needs time to heal or to divert colonic contents from an inflamed segment prior to intervention. A low anterior resection may be performed for carcinoma of the proximal and mid rectum with a deep pelvic anastomosis of proximal colon and distal rectum. Abdominoperineal resection involves rectal resection and a permanent colostomy. Pelvic exenteration may be performed for extensive rectal cancer requiring resection of the pelvic organs including the rectum. A colostomy and ureterostomy is then required. Typically, mild-to-moderate uptake will be seen at the stoma (147).

The Hartmann procedure requires a diverting colostomy leaving a blind-ending rectal or colonic stump closed by sutures. It is usually performed as an emergent procedure for severe complicated diverticulitis, obstruction, or perforation sigmoid colon or trauma (148). Subsequently, the bowel can be reanastomosed.

Ileoanal pouch-anal anastomoses may be performed to treat UC or familial polyposis. The procedure involves resection of the entire colon and complete transanal mucosectomy leaving a short rectal cuff. An ileal pouch

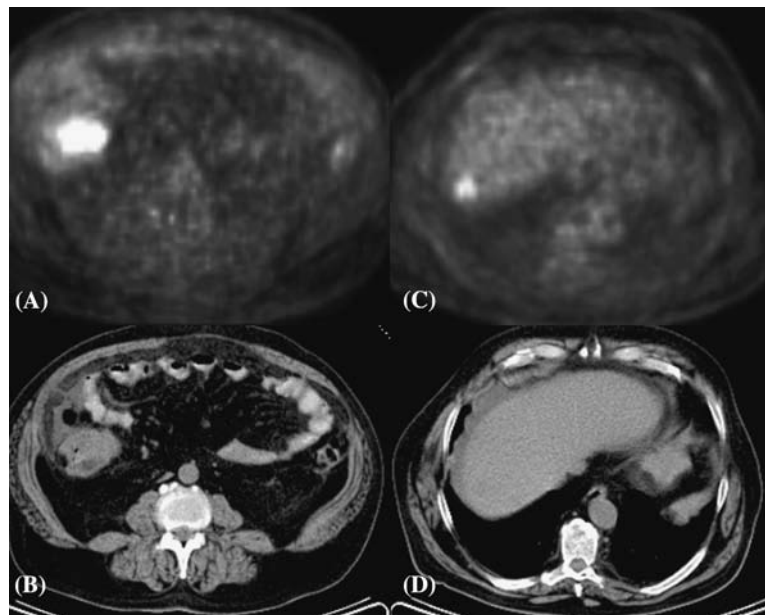


Figure 27 PET/CT performed for staging in a patient with a right-sided colon carcinoma. FDG PET (A) shows the uptake corresponding to the ascending colon mass on the registered CT (B). The study also showed a focus of uptake in the liver (C) corresponding to a hypodensity on unenhanced CT (D) compatible with liver metastasis. Note the ascites on the unenhanced CT. *Abbreviations:* PET/CT, positron emission tomography/computed tomography.

is created most commonly using two loops of small intestine in a J configuration and anastomosed to the rectal cuff. This task may be performed in a one-stage or two-stage procedure, i.e., without or with a diverting ileostomy, although a one-stage procedure is preferable. Complications such as anastomosis leak, abscess, perforation, and recurrence, if performed for neoplasm, should be excluded. Formation of granulation tissue and postsurgical inflammation/edema may mimic recurrence on CT. While uptake on FDG PET, indistinguishable from recurrence, may persist at the anastomotic site (149), this uptake should decrease in intensity over time.

Recurrence

Since resection of recurrence at the primary site, liver metastases, or even solitary pulmonary metastases appears to be associated with a better outcome for patients with a history of colorectal cancer, identification of the site and extent of recurrence is critical for management (150). While resection of portal lymph node metastases does not affect prognosis after recurrence, the eradication of peritoneal disease may have a better result (150).

Recurrence postsurgery may present on CT as a soft tissue mass at the site of surgery, although hematoma, fibrosis, or incomplete distention may mimic tumor recurrence. Metastases commonly occur in the liver, lung, adrenal glands, and bones (Fig. 26). The use of CT in detection of recurrence has an overall accuracy of 25% to 73%, and may miss up to 7% of hepatic metastases. In addition, CT may underestimate the number of hepatic lobes involved in up to 33% of patients. Further challenges lie in visualizing all metastases to the peritoneum, mesentery, and lymph nodes, as well as in differentiating postoperative changes from recurrence, which is often equivocal. Of the patients with negative CT up to 50% will have nonresectable lesions at laparotomy.

PET has demonstrated an overall sensitivity of 90% and specificity greater than 70% in the diagnosis of recurrence. It is able to use metabolic information to distinguish scar from local recurrence with greater than 90% accuracy, although occasionally granulomatous change at the anastomosis may give a false positive (149). In another series of patients studied with PET, CT, and then with fused PET and CT, the accuracy of registered PET/CT images improved the accuracy of pinpointing the site of recurrence from 78% to 79% with either modality alone to 92% (151).

In a study of 76 patients, the accuracy of CT in recurrence detection was 65% versus 95% for PET (152). In patients with a clinical or radiologic suspicion of disease but with a negative CEA, PET has shown a positive predictive value of almost 85% and an accuracy of about 76% (153). In the setting of rising serum CEA postresection of the primary, with no abnormalities on

conventional work-up, FDG PET has sensitivity of 93% to 100%, and specificity up to 92% (154–156). In addition, PET will demonstrate tumor in two-thirds of patients with a rising CEA (155,156) and permit a successful surgical treatment of recurrence in over 80% of those patients (154). The amount of PET positive tumor seems to correlate with degree of elevation of CEA (157).

Comparison of sensitivity and specificity of FDG PET and CT for detection of recurrence or metastatic disease by particular anatomic locations finds that PET is more sensitive except in the lung, where the two were equivalent, likely secondary to decreased resolution on PET for smaller nodules because of respiratory motion. In the evaluation of hepatic metastases, a meta-analysis comparing noninvasive imaging for detection of hepatic metastasis from colorectal, gastric, and esophageal cancers demonstrated that at equivalent specificity of 85%, FDG PET had sensitivity of 90% in comparison with MRI 76%, CT 72%, and US 55% (1). Another review of the literature has found a pooled sensitivity for liver metastases of 79% for PET and specificity of 92% compared with CT sensitivity of 83% and CT specificity of 84% (158). Even with a negative CEA, PET has shown a positive predictive value of almost 89% for the presence of liver metastases (153).

PET can detect extrahepatic disease in a sixth of patients with liver disease but without evidence of extrahepatic disease on conventional imaging (150). While PET may be comparable or better with hepatic disease, it is more consistently helpful with extrahepatic disease. The largest discrepancy occurs in the abdomen, pelvis, and retroperitoneum where one-third of PET positive lesions were negative by CT. PET was also more specific than CT in all sites except the retroperitoneum; however, these differences were smaller than those seen in sensitivity (155). In a review of the literature, PET showed a greater sensitivity (91%) compared with CT (61%) (158).

PET/CT compared with PET alone does not appear to improve detection of intra-abdominal extra-hepatic recurrences significantly, but does augment PET alone in the detection of extra-abdominal recurrences and intrahepatic metastases with a sensitivity of 89% compared with 80% for PET alone, specificity of 92% compared with 69% for PET alone, and accuracy of 90% compared with 75% in a series of 84 patients with recurrent colorectal cancer (159). In another study of 51 patients with known recurrences, PET/CT improved the accuracy of PET alone from 71% to 88% (160). Even in the previously irradiated patient with a history of rectal cancer, PET has shown high sensitivity (84%), specificity (88%), and accuracy (87%) in identifying the presence and nature of the recurrence with particularly good negative predictive value (161). Therefore, overall FDG PET and especially PET/CT are useful in distinguishing local recurrence from postoperative changes, identifying hepatic metastases,

classifying indeterminate pulmonary nodules, demonstrating nodal involvement, and providing a whole-body survey for metastatic lesions. Because of this, PET and PET/CT commonly alter management of patients with identified recurrent colorectal cancer, reportedly one-fourth to one-third of patients (158,162,163).

Monitoring treatment response

Decreased FDG uptake without immediate decrease in lesion size on CT either during or following therapy indicates response to treatment (164). Radiation therapy presents challenges in the form of immediate posttreatment inflammation; however, FDG PET can assess residual tumor versus scarring (135) on the basis of the pattern of uptake as well as the degree of metabolic activity. Postradiation type changes are generally diffuse and non-focal in nature in contradistinction to viable tumor, which is more focal and more intense. Delay of posttherapy PET scan to six or more weeks following radiation increases specificity (161).

PET/CT is also useful in predicting response to chemotherapy in the midst of, as well as after, completion to evaluate for residual viable tumor. Patients with hepatic metastases had accurate PET/CT prediction of response to five weeks of fluorouracil therapy based on pretreatment FDG uptake as well as during therapy (Fig. 28) (165). Current research strives to establish more definitive guide-

lines for prediction of response to preoperative chemo/RT using specific SUVs.

Metastases to Colon

Metastases may reach the colon by direct extension, intraperitoneal seeding, or hematogenously. Direct extension may occur from contiguous prostate, ovarian, or renal cell carcinoma. Tumors of the stomach and pancreas may spread by direct extension via lymphatics or along the peritoneal spaces. Intraperitoneal seeding can occur with ovarian, gastric, pancreatic, and colonic carcinomas. Mucinous adenocarcinomas of the appendix, described as pseduomyxoma peritonei, can spread intraperitoneally. Like ovarian cancer, metastases from mucinous adenocarcinoma of the appendix or other locations are low density appearing cystic or fluid density and may cause ascites. Mucinous primary tumors often demonstrate metastatic foci with calcification. Hematogenous spread occurs with malignant melanoma, breast, and lung cancer.

Endometriosis is a gynecologic disease defined by ectopic foci of endometrial tissue outside the uterine cavity. Endometrial implants along the serosal surface of the colon may mimic metastases. They may appear as soft tissues or cystic masses that are typically extrinsic or serosal in location, but can be intramural. They are most commonly located in the rectosigmoid, rectovaginal

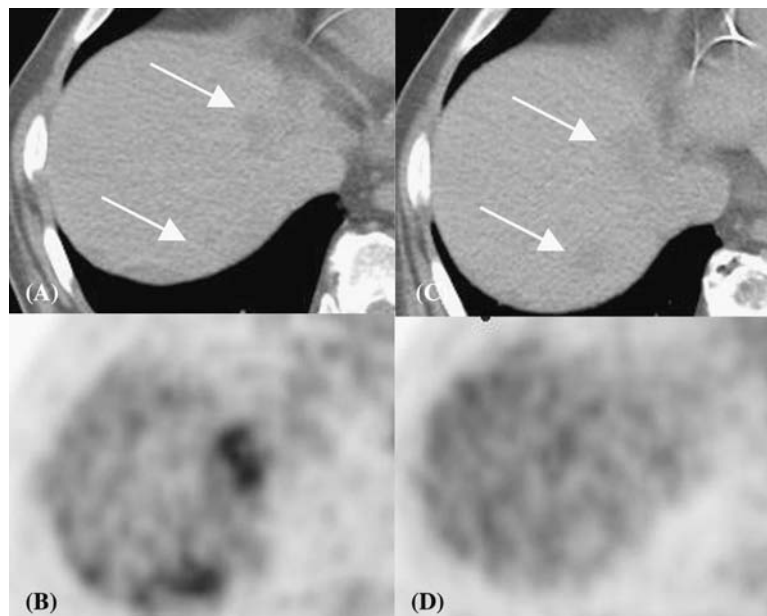


Figure 28 A 75-year-old man with metastatic colon disease studied with PET/CT in June (**A–B**) for evaluation of extent of disease. Unenhanced axial CT (**A**) shows hypodensities in the liver that correspond to two foci of increased uptake on the FDG PET (**B**) with maximum SUVs of 4.2 and 4.7, respectively, consistent with metastases. Five months later, after chemotherapy a repeat study showed persistence of smaller hypodensities in the liver (**C**) but complete resolution of the metabolic abnormalities on PET (**D**). The relatively low SUV of the metastases predicts the metabolic response seen on the follow-up PET. *Abbreviations:* PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value.

space, small bowel, cecum, or appendix and can cause luminal narrowing and obstruction.

SOLID ORGANS

Technical Pearls for Imaging the Liver and Abdominal Viscera

Dynamic liver imaging using a combination of unenhanced and IV contrast-enhanced CT imaging is preferable for assessing certain benign and malignant neoplasms. Imaging the liver in an arterial, portal venous, and, occasionally, a delayed phase permits the interpreting physician to better characterize focal liver lesions. This may not be possible in the context of the routine PET/CT examination. However, narrowing the window and level setting at a workstation helps increase the conspicuity of liver lesions, and this is available on conventional PET/CT viewing software.

Dynamic imaging is also helpful for assessment of pancreatic, renal, and even adrenal lesions. The spleen demonstrates inhomogenous patterns of enhancement that are variable in the arterial phase of imaging and may be mistaken for focal masses or infarct and it is important to become familiar with the range of enhancement patterns of the spleen, and to recognize the phase of enhancement to improve interpretation.

Liver

Normal Anatomy

Liver may be divided into segments on the basis of the vascular tree. The right hepatic vein divides the anterior and posterior right hepatic lobes, the middle hepatic vein divides the right and left lobes, and the left hepatic vein divides the medial and lateral segments. It may be further divided by a numbering system based on Couinaud's segments and the Brisbane 2000 Terminology (166). Segment 1 refers to the caudate, segment 2 the superior portion of the lateral segment, segment 3 the inferior portion divided by the left portal vein, segments 4a and 4b the medial segment left lobe superior and inferior aspects divided by the portal vein, segments 5 and 8 represent the anterior inferior, and superior right lobe and segments 6 and 7 the posterior inferior and superior right hepatic lobe segments with superior and inferior portions delineated by the right portal veins (Fig. 29). Additional anatomic landmarks include the falciform ligament and ligamentum teres, which is a cleft that divides the medial and lateral segments of the left lobe.

In the setting of portal hypertension the paraumbilical vein a fetal remnant may recanalize secondary to portal hypertension. The ligamentum venosum courses posterior to the left-lateral lobe segment and anterior aspect of the

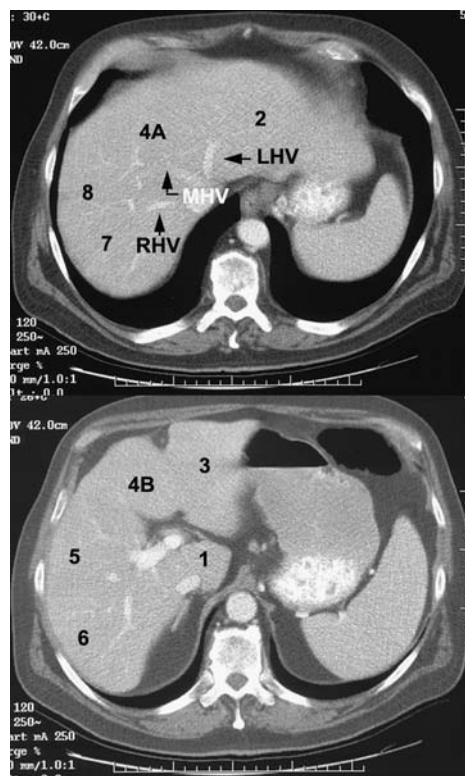


Figure 29 (Upper image) CT scan through the liver above the portal vein shows superior Couinaud segments. The numbers in the image indicate the following: 7, posterior inferior segment right lobe; 8, anterior superior segment right lobe; 4A, medial superior segment of the left lobe; 2, superior portion of the lateral segment of the left lobe. (Lower image): CT through the liver below the portal vein shows the inferior Couinaud segments. The numbers in the image indicate the following: 1, caudate lobe; 3, inferior lateral segment of the left lobe; 4B, inferior medial segment of the left lobe; 5, anterior inferior segment of the right lobe; 6, posterior inferior segment of the right lobe. Abbreviations: CT, computed tomography; MHV, middle hepatic vein; LHV, left hepatic vein; RHV, right hepatic vein.

caudate. The caudate is interposed between the intra-hepatic portion of the IVC and the main portal vein. Both the caudate and lateral segment of the left lobe may hypertrophy in the setting of cirrhosis depending on the underlying etiology, and there is typically medial left-lobe atrophy with apparent widening of the gallbladder fossa.

Liver parenchyma is normally 40–65 HU and is slightly denser than spleen by about 10 HU on unenhanced CT. Depending on the timing of contrast infusion, parenchyma may vary in density measurements. On early arterial phase imaging, the hepatic artery may be visualized but the parenchyma does not enhance significantly until the portal venous phase because the vast majority of blood supply to the liver comes from the portal circulation. Hepatic veins



Figure 30 Patient with a history of recurrent gastric cancer treated with external beam radiation. The left lobe of the liver, which was in the radiation port, now shows atrophy.

will not opacify completely until slightly later depending on patient's circulation time and unopacified hepatic or portal veins should not be mistaken for thrombosis. Surgical intervention may distort liver morphology following segmental resection, radiofrequency ablation, cryotherapy, or chemoembolization. Following partial resection, the remaining liver may regenerate and appear enlarged. Familiarity with the normal venous and segmental liver anatomy is helpful when determining if prior liver surgery was performed. Atrophy may develop in the lateral segment of the left lobe, e.g., postradiation therapy with focal changes within the confines of the radiation port (Fig. 30).

The liver demonstrates diffusely increased FDG activity physiologically and is used as a qualitative comparison point for other foci of uptake in the body, so that activity that is equal or greater than the liver raises concern for pathologic processes. Mild heterogeneity is usually present and is also physiologic. It is important to differentiate between small foci, which may represent early malignancy, and the heterogeneous nature of the liver parenchyma. Also, respiratory motion and subsequent

misregistration makes the liver a common site of artifact on attenuation corrected images.

Diffuse Disease

Hepatomegaly is defined as enlargement greater than 15 cm in the craniocaudal dimension. Normal variation may occur with elongation of the right lobe seen in women called Reidel's configuration or the left lobe may extend in the left-upper quadrant and overlie the spleen.

Fatty liver or hepatic steatosis can result from many causes, most commonly alcoholic liver disease, obesity, diabetes mellitus, malnutrition, parenteral nutrition, chronic illness, hepatitis, chemotherapeutic agents, radiation, and steroid use. On unenhanced CT, liver decreases in density compared with the spleen greater than 10 HU. On enhanced CT, diagnosis is more difficult because density of the liver and spleen depends on phase of contrast enhancement; a limit of greater than 20 HU may be used but can vary. Confirmation with MRI may be performed using chemical shift imaging. Fatty infiltration of the liver may be diffuse or focal and may demonstrate areas of focal fat-sparing mimicking focal masses. Common locations for focal fatty infiltration or sparing are adjacent to the gallbladder fossa and anterior to the porta hepatis (Fig. 31). Normal vasculature runs through these regions unlike a mass, which should displace normal vessel. MRI may be warranted to assess for unusual patterns of fatty replacement or sparing.

Cirrhosis and Portal Hypertension

Cirrhosis most commonly is a result of viral infection or alcohol abuse, but may occur in response to medications, toxins, hepatic congestion, hemochromatosis, biliary diseases, or hereditary diseases. Pseudocirrhosis may occur in patients with diffuse metastases or following treatment

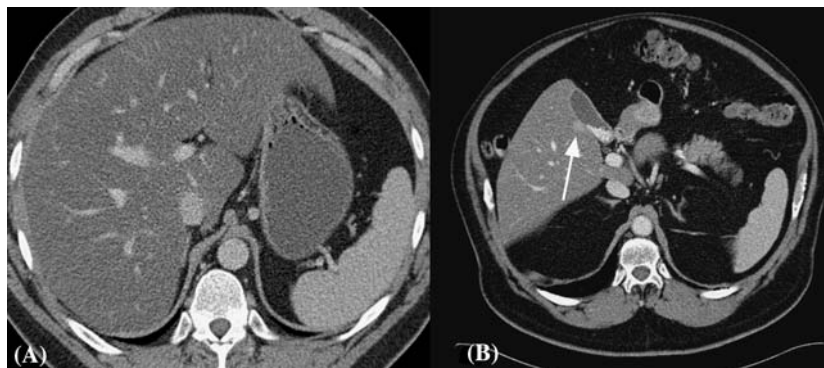


Figure 31 (A) Axial contrast-enhanced CT scan performed in an obese, diabetic patient shows a diffuse low-attenuation liver compared with the spleen. (B) There is a small area of sparing (arrow) adjacent to the gallbladder fossa that shows higher density than the remainder of the fatty liver. *Abbreviation:* CT, computed tomography.

with chemotherapeutic agents often seen in women with breast cancer metastases (Table 13). For the most part, increased uptake on PET will differentiate between these entities. Idiopathic portal hypertension and hepatic necrosis following fulminant hepatitis may also demonstrate features of cirrhosis (167). Morphologic features of cirrhosis can vary depending on degree but may include: atrophy of the central liver leading to expansion of the gallbladder fossa and porta hepatis, which fills in with fat secondary to the atrophy, hypertrophy of the lateral segment or caudate, shrunken liver, nodular contour or nodular parenchyma, fibrosis with fibrosis septations surrounding nodule either regenerative or dysplastic, and peribiliary cyst (Fig. 31).

Associated signs of portal hypertension include splenomegaly, ascites, and portosystemic collaterals including gastroesophageal varices, recanalization of the paraumbilical vein, splenorenal shunting, retroperitoneal, and perirectal varices. With development of portal hypertension, there is a shift in blood supply with hepatic arterial supply increases such that the hepatic artery may enlarge and become more tortuous because of high pressures in the liver. Portal vein may become engorged along with the SMV and splenic vein because of increased pressures in the liver. Portal vein may occlude with bland or tumor thrombus, and collaterals may develop that surround the portal vein, porta hepatic, or gallbladder and mimic a mass. Again, dynamic contrast-enhanced imaging may be useful to distinguish collateral vessels from a pseudomass. The cirrhotic liver is not FDG avid (168), but PET has been found useful in monitoring children with cirrhosis for intrahepatic infections while awaiting transplantation (169).

Table 13 Cirrhosis and Portal Hypertension

Causes of cirrhosis	Viral infection
	Alcohol abuse
	Medications
	Toxins
	Hepatic congestion
	Hemachromatosis
	Biliary disease
	Hereditary disease hemachromatosis
	Wilson's disease
Causes of pseudocirrhosis	Extensive hepatic metastases
	Post treatment for metastatic disease
	Fulminant hepatic necrosis
Morphologic features	Atrophy of the central liver
	Expansion and fat in the gallbladder fossa and porta hepatic
	Shrunken liver
	Nodular liver contour
	Nodular liver parenchyma
	Fibrosis
	Fibrous septations

Hepatitis

There are no specific signs of hepatitis on CT although there may be hepatomegaly and periportal edema manifested by periportal low attenuation, not to be confused with biliary duct dilation. Periportal edema is seen on both sides of the portal veins rather than anterior to the portal veins as seen with biliary duct dilation. On an early arterial phase there may be patchy enhancement patterns. FDG PET is generally negative in the liver, but may be useful to help evaluate hepatocellular carcinoma (HCC) for which hepatitis B carriers are at risk (170). Lymphadenopathy in the periportal space may also be present. This may be FDG_avid on PET (171) and must be distinguished from metastatic lymph nodes in the setting of a known primary cancer.

Focal Liver Disease

Infection

Hepatic abscesses

Pyogenic abscesses may develop from sepsis, cholangitis, local extension of infection, or trauma. On unenhanced CT, there may be low attenuation, a thick rim, or septations and may contain gas. On contrast-enhanced CT, there is usually a thick rim of enhancement, septal enhancement if more complex or multiloculated, and may be associated with hyperemia of surrounding liver parenchyma on early artery phase imaging. They may be solitary or multiple, and may lead to portal or hepatovenous thrombus, and they may be positive on FDG PET (172).

Nonpyogenic abscesses

Amebic abscesses are nonspecific in appearance presenting as a unilocular mass with a hypopattenuating rim more often located in the right lobe of the liver. The rim of the abscess enhances following contrast administration. Enhancement may be smooth or nodular.

Hydatid cysts

Although unusual, echinococcal or hydatid cysts have a more distinct appearance on CT. These cysts may be unilocular but more typically contain a larger “mother” cyst centrally with daughter cysts peripherally. The cysts may contain fluid of different densities. There may be enhancement of septations and the cyst wall. Calcification may appear as high attenuation in the wall or in septations. On FDG PET echinococcal cysts will be metabolically active when disease is active (173,174), but FDG avidity will decrease with successful medical treatment (173,174).

Fungal abscess

These tend to occur in immunocompromised patients and are often small low-attenuation lesions with rim enhancement difficult to differentiate from metastases, lymphoma, or sarcoidosis. The most common etiology is *Candida albicans* but *aspergillus* and *cryptococcus* may be seen. Other organs such as the spleen and kidneys may be involved. Granulomatous lesions like these have been positive on FDG PET and mostly reported as false positives for tumor (172).

Noninfectious Inflammation

Sarcoidosis is a granulomatous disease that may involve the lung, mediastinal, and retroperitoneal lymph nodes, kidney, liver, and/or spleen. It can cause hepatic and splenic enlargement as well as multiple, small, less than 2 cm hypoattenuating nodules in the liver and spleen and may mimic lymphoma. Liver may demonstrate hypoattenuating intrahepatic septa rather than discrete nodules. Splenic lesions may become confluent, giving an infiltrative appearance. FDG PET has been reported to show fairly intense metabolic activity in these lesions (175). Although delayed imaging may help with nongranulomatous infection, this is not the case with sarcoidosis (176). Although not generally available in the clinical setting, ^{18}F alpha methyltyrosine is negative in sarcoidosis but not in tumor and theoretically might be helpful in distinguishing the entities (175). Nonetheless, for the time being, chest CT is helpful to identify typical pulmonary findings of sarcoidosis. Biopsy may be required.

Benign Liver Tumors

Hepatic cysts

Hepatic cysts are low attenuation less than 10 HU, lesions but may be difficult to characterize if less than 1 cm. Cysts may be multiple, contain thin septations and lobulated margins. They may contain hemorrhage or proteinaceous debris and become high density so that pre- and postcontrast imaging is required either with CT and MRI to confirm the absence of enhancement. Multiple cysts occur commonly. On PET/CT, cysts large enough to resolve spatially will be hypometabolic (177) and on CT they will tend to have HU less than 30. Infected cysts will demonstrate metabolic activity, however.

Cavernous hemangioma

Hemangiomas are the most common benign liver tumor and occur more frequently in women. They may be solitary or multiple. On unenhanced CT they are low attenuation similar to a cyst. Only on contrast-enhanced imaging can the diagnosis be made (Fig. 32). Dynamic multiphase imaging is useful. The classic features usually seen in hemangiomas less than 3 cm include peripheral nodular enhancement, which progressively fills in a centripetal pattern on delayed phase imaging (178). Large or larger than 4 cm hemangiomas may not be completely filled in with contrast or demonstrate a central hypovascular fluid density scar. Rapid- or flash-filling hemangiomas are usually smaller than 1 cm, enhance homogeneously on the arterial phase and will continue to enhance on delayed phases paralleling the attenuation of contrast within the

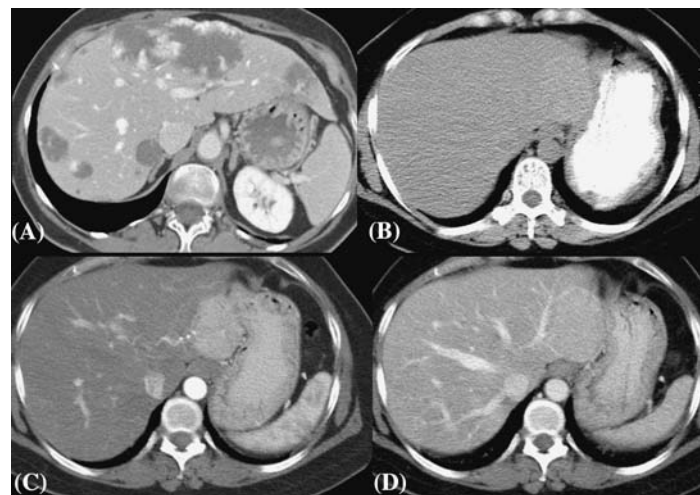


Figure 32 (A) Contrast-enhanced CT in a patient with multiple cavernous hemangiomata showing peripheral, nodular enhancement of the lesions. (B) Unenhanced CT performed in another patient with FNH in the left lobe of the liver shows a subtle hyperdense lesion in the left lobe. (C) On the arterial phase of the contrast-enhanced study, there is rapid enhancement of the FNH with a feeding vessel. (D) On the portal-venous phase, the lesion is now almost isointense relative to the liver. *Abbreviations:* CT, computed tomography; FNH, focal nodular hyperplasia.

aorta. T2-weighted and dynamic contrast-enhanced MRI can help for further characterization. Occasionally, hemangiomas will contain calcification or phleboliths and may thrombose. Hemangiomas have been reported to be metabolically inactive on FDG PET imaging (170).

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is a rare tumor but is the second most common benign tumor after hemangioma, and usually occurs in younger female patients. This entity may be seen in association with hemangiomas. On unenhanced CT, these lesions are homogeneously isodense to slightly hypodense relative to liver and will not usually be apparent. Following administration of contrast, however, they will enhance briskly and homogeneously on the early arterial phase images, becoming more isodense relative to normal surrounding liver parenchyma on the portal venous phase (Fig. 32). The larger lesions may exhibit a characteristic central scar, which lacks enhancement. Radiating fibrous bands or septae is another classic yet infrequent finding (179). A pseudocapsule may be seen or a feeding hepatic artery or draining vein may be present. These lesions can also be multiple. While most FNH is hypometabolic or isometabolic with the liver on FDG PET (180), occasionally these lesions may demonstrate increased activity relative to the liver (181).

Hepatic adenoma

Hepatic adenomata are uncommon benign tumors more frequently seen in women on oral contraception. On unenhanced CT, these lesions are variable in density depending on the presence or absence of hemorrhage. These lesions are susceptible to hemorrhaging particularly if they are large. They tend to contain microscopic fat as well, which can be identified on chemical shift MRI. On contrast-enhanced CT, they demonstrate homogenous arterial enhancement slightly less brisk than FNH and tend to be homogenous but slightly hypodense to liver on delayed imaging occasionally associated with a thin enhancing rim or capsule. On PET, hepatic adenomas have been described as relatively hypometabolic (182).

Fat-containing lesions

Macroscopic fat density lesions (Table 14) are rarely seen in the liver but are typically benign, such as angiomyolipomas, lipomas, or extramedullary hematopoiesis. Rarely, a fatty tumor such as liposarcoma will lead to fat-containing liver metastases. Focal fat may be seen normally adjacent to the IVC near the diaphragmatic hiatus. HCC may contain fat but typically small amounts of fat that are only detected on MRI.

Table 14 Focal Lesions of the Liver with Fat or Calcification

Fat-containing focal lesions	Focal lesions with calcification
Angiomyolipomas	Prior granulomatous disease
Lipomas	Hemangiomas
Extramedullary hematopoiesis	Abscesses
Liposarcoma metastases	Prior trauma
Focal fat at the IVC	HCC
HCC (microscopic)	Metastases
Hepatic adenoma (microscopic)	

Abbreviations: IVC, inferior vena cava; HCC, hepatocellular carcinoma.

Calcification

Small calcifications may be solitary or multiple, and if not associated with a discrete mass, are likely due to prior granulomatous disease. Hemangiomas may contain calcification, usually phleboliths. Abscesses may contain wall or septal calcification. Calcification may occur as a result of trauma. HCC and metastases may contain calcification but are associated with a discrete mass.

Malignant Tumors

Hepatocellular carcinoma

HCC is usually seen as a complication of viral hepatitis and cirrhosis but may occur in a noncirrhotic liver. HCC may be solitary, multifocal, or diffusely infiltrating. Dynamic contrast-enhanced imaging is crucial to diagnosis. MRI has advantages over CT particularly for diagnosing small HCC; although, small HCC may still go undetected by either technique despite optimized technique. Precontrast imaging is helpful as well, particularly if a lesion has been treated. Treated lesions may contain calcification or be hyperdense because of chemoembolization material, and this should not be confused with hyperdensity related to true-contrast enhancement. In the setting of cirrhosis many nodules may actually be regenerative and dysplastic nodules.

HCC has variable patterns of enhancement from hypervascular to hypovascular depending on the lesion and timing of contrast enhancement. Classically, HCC are hypervascular on arterial phase imaging and a small lesion may only be seen on the early phase. On later phases the lesion may become iso- to hypodense with rim enhancement described as “washout.” HCC may grow into the hepatic, portal veins, and IVC or be associated with bland thrombus (Figure 33). Large HCC may develop areas of necrosis or hemorrhage. Fibrolamellar HCC is an uncommon histologic subtype that tends to occur in younger patients without liver disease and may mimic FNH. They are large, well circumscribed, sometimes lobular, and homogeneously enhancing masses, which may demonstrate



Figure 33 (A–B) Noncontrast CT in a patient with cirrhosis and HCC. The liver shows nodularity of the contour of the liver and lateral segment hypertrophy consistent with cirrhosis. Unenhanced CT demonstrates a large hypodense mass in the right lobe with distention of the portal vein (A–B). Arterial phase images from a contrast-enhanced CT (C–F) reveal arterial enhancement in the large HCC with enhancing tumor thrombus in the right and main portal veins. Note the heterogeneity of the spleen, a normal appearance in the hepatic arterial phase of imaging. *Abbreviations:* CT, computed tomography; HCC, hepatocellular carcinoma.

central calcification or an enhancing scar on delayed imaging.

FDG PET imaging of HCC is somewhat limited because of the activity of glucose-6-phosphatase in higher amounts in this tumor (183,184). Recall that glucose-6-phosphatase dephosphorylates glucose allowing for its transport out of the cell. In a similar manner, this enzyme acts upon FDG and can create the outflow of the radiopharmaceutical, thereby limiting accurate imaging and appropriate detection of a tumor that expresses it. HCC is more FDG avid than the liver in approximately 55% of cases; it is equal to or less avid in 30% and 15% of cases, respectively. PET detects only 50% to 70% of HCCs (182,185) but is useful in detection of distant metastases as well as in evaluation of recurrence.

Initial staging of hepatocellular carcinoma

In FDG-avid HCC, PET/CT imaging is valuable to staging, especially in the assessment of distant metastatic

disease. Studies have illustrated detection rate of 83% for extrahepatic metastases larger than 1 cm and 13% for lesions less than or equal to 1 cm (186).

Monitoring of therapy and detection of recurrence

Currently PET may be useful in assessing therapy including ablation of HCCs using various techniques. Following treatment response using only anatomic imaging may limit assessment of residual viable tumor, and the role of FDG PET is suggested to assist in guidance of further therapy (187,188) by detecting metabolically active tissue. In order to limit confounding factors such as post ablation inflammation, a delay of several weeks is recommended following therapy. Current research seeks to establish more definitive guidelines for the evaluation of posttherapy HCC using FDG PET.

Similarly, in the detection of recurrence, PET plays a role in discovering metabolically active tumor prior to the development of anatomic evidence on conventional

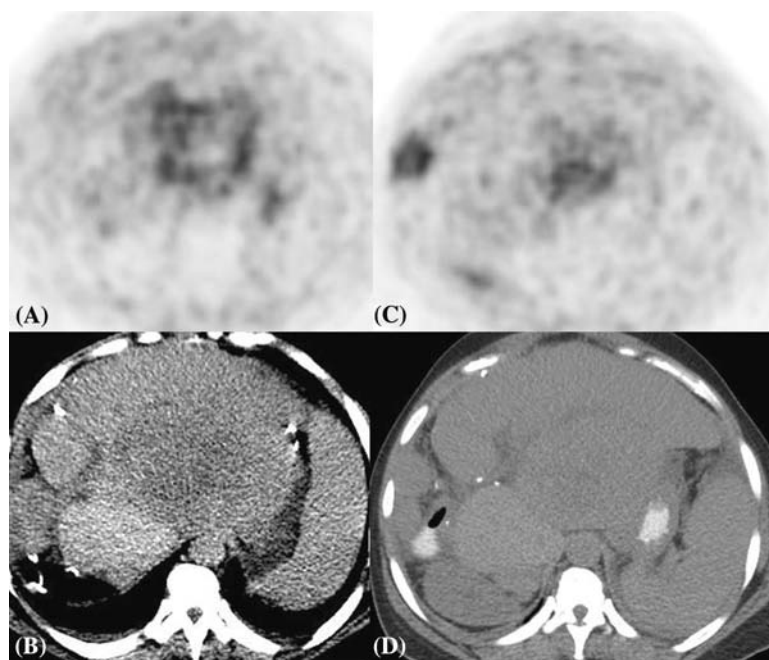


Figure 34 Patient with recurrent hepatocellular carcinoma. (A) FDG PET from a PET/CT shows heterogeneous uptake in the enlarged left lobe. (B) Corresponding axial image from an unenhanced CT shows an ill-defined hypodensity (*white arrow*) corresponding to this area of uptake as well as surgical clips from the prior partial hepatectomy and a hyperdense lesion likely a postoperative hematoma (*arrowhead*) with no corresponding FDG uptake. Corresponding axial PET/CT images (C,D) slightly more inferiorly demonstrate a peripheral focus of uptake corresponding to a soft tissue mass on CT (D) (*black arrow*) compatible with a peritoneal implant. *Abbreviation:* PET/CT, positron emission tomography/computed tomography.

imaging. Evaluation of patients with elevated serum alpha-fetoprotein levels after the treatment of HCC and negative conventional imaging work-ups suggests a sensitivity, specificity, and accuracy of FDG PET for detecting HCC recurrence of 73.3%, 100%, and 74.2%, respectively (189).

Overall, most metastatic tumors are FDG avid and readily detectable using PET/CT (Fig. 34). A fraction of HCCs demonstrate increased radiopharmaceutical uptake and may be assessed using metabolic imaging. Approximately one-third of HCCs and most benign processes do not accumulate increased amounts of FDG and, therefore, cannot be reliably assessed using PET/CT. Currently, PET/CT is not indicated in the screening of patients who are at increased risk for HCC or in the evaluation of focal hepatic lesions in the setting of chronic hepatitis C, which can obscure minimal uptake in a malignant focus.

Metastases to the liver

Metastases to the liver occur more frequently than primary hepatic malignancy and typically arise from colorectal, gastric, pancreatic, lung, and breast carcinomas. Nonetheless, small benign liver masses are common, and in the setting of malignancy very small masses are still likely to be benign (190,191). Metastases are variable in appearance but there are some patterns that help narrow the differential diagnosis (Table 15). The majority of liver

metastases are iso- to hypoattenuating relative to liver on unenhanced CT imaging, and hypoattenuating relative to liver parenchyma on the portal-venous phase of contrast enhancement (Figs. 25–27).

Cystic metastases are common in ovarian, colon, and pancreatic neoplasm and may mimic benign cysts. Subtle rim enhancement or nodularity would favor metastases but prior imaging for comparison to assess for interval change is most helpful. Calcifications may be present in mucinous adenocarcinoma metastases from GI origin such as colon, pancreas or stomach, ovarian carcinoma, thyroid, renal, and neuroblastoma. Hemorrhagic metastases may be seen in melanoma. Both hemorrhage and calcification are best assessed on unenhanced CT. Low-density metastatic lesions are seen in lymphoma and may mimic abscess or sarcoidosis. Hypervascular metastases are lesions best seen on the arterial phase of imaging but poorly seen on the portal venous phase including HCC, renal cell carcinoma, carcinoid, islet cell tumors, thyroid cancer, melanoma, sarcomas, and choriocarcinoma. If a patient has a known hypervascular primary tumor, dynamic multiphase imaging is recommended as metastases may be missed if only portal venous phase imaging is performed. Breast cancer metastases may be better seen on unenhanced CT such that imaging protocols for these cases often include unenhanced imaging through the liver

Table 15 Distinguishing Features of Liver Metastases

Feature	Primary	Differential (dx)
Cystic metastases	Ovarian	Benign cyst
	Pancreas	Hemangioma
	Gastric	Biliary cystadenoma
	Sarcoma	Biliary hamartomas
	Melanoma	Hydatid cyst
	Lung	Caroli's disease
	Necrotic metastases	
Calcifications	Mucinous carcinoma of the GI tract, e.g., colon, pancreas, stomach	Granuloma
	Ovarian carcinoma	Calcified thrombosed
	Thyroid	Hemangioma
	Renal	Pseudocyst
	Neuroblastoma	Hydatid cyst
	Osteosarcoma	
	Melanoma	
	Testicular	
Hemorrhagic	Melanoma	Hemorrhagic cyst
Low density	Lymphoma	Abscess
		Sarcoidosis
		Cyst
		Hemangioma
Hypervascular ^a	Hepatocellular carcinoma	Hepatic arterial
	Renal cell carcinoma	Pseudolesion
	Carcinoid	Arterioportal shunt
	Islet cell tumors	Flash filling hemangioma
	Thyroid cancer	Focal nodular
	Melanoma	Hyperplasia
	Sarcomas	Hepatic adenoma
	Choriocarcinoma	
	Colon cancer	

^aBest evaluated with dynamic multiphase imaging

Abbreviation: FNH, focal nodular hyperplasia.

followed by portal venous phase imaging to assess the rest of the abdomen and pelvis.

With PET/CT usually an unenhanced or a single enhanced phase of imaging is obtained through the liver limiting the sensitivity for lesion detection and characterization. If an indeterminate lesion is found on PET/CT further imaging with dynamic CT or MRI is recommended depending on availability of patient's age, renal function, and any potential contraindications to iodinated contrast agents or to MRI. MRI is extremely useful for characterization of all types of liver lesions and may be superior to other modalities for detection and characterization of smaller lesions.

Most liver metastases are hypermetabolic on FDG PET, including adenocarcinomas, sarcomas, melanomas, adrenal cortical carcinomas, and cholangiocarcinomas (182,192,193). While it is well accepted that FDG PET/CT has a role in detecting liver metastases, some of the newer techniques in MRI may augment or replace PET/CT.

However, even when MRI techniques might improve on PET/CT sensitivity, PET/CT tends to be more specific and also to demonstrate extrahepatic metastases better (194,195).

More recently, there has been a great deal of evidence to suggest that FDG PET/CT is particularly useful in the evaluation of treatment response in liver metastases, whether it be after chemotherapy, radiofrequency ablation, or treatment with radiolabeled glass spheres (196–199). However, in the assessment of neoadjuvant therapy, a negative PET/CT should not be taken as evidence of a pathologic response and resection should still be performed (198).

Cholangiocarcinoma

Cholangiocarcinoma is the second-most common primary liver malignancy after HCC. It can be a complication of primary sclerosing cholangitis (PSC) (which can be associated with ulcerative colitis) and *Clonorchis sinensis*

infection, among other risk factors. In patients with primary sclerosing cholangitis, cholangiocarcinoma is not necessarily a late event and in fact usually precedes cirrhosis. Twenty to thirty percent of patients will already have cholangiocarcinoma at the time their PSC is diagnosed (200). FDG PET has not played a significant role in screening these patients (200). Cholangiocarcinoma is typically a fibrous tumor that is associated with desmoplastic reaction, which influences its imaging appearance. These tumors obstruct the bile duct and cause intrahepatic biliary duct dilatation. Cholangiocarcinoma tumor may be extrahepatic or intrahepatic, peripheral or hilar/central. Hilar carcinomas are also known as Klatskin tumors and occur at the bifurcation of the common hepatic duct. Peripheral cholangiocarcinoma is typically a large hepatic mass with lobulated margins that is heterogeneous but low attenuation with rim enhancement (201). On delayed imaging, there may be persistent enhancement and associated capsular retraction as well as thickening along dilated biliary ducts. Hilar carcinomas are typically infiltrative but may be exophytic or polypoid. They present with focal thickening of the duct wall and are hyperattenuating to the liver particularly on delayed contrast-enhanced CT. Since these tumors accumulate FDG, PET/CT is particularly useful for staging lymph nodes and identifying peritoneal disease to determine resectability (202,203).

Pancreas

Normal Anatomy

The pancreas lies posterior to the stomach anterior to the spine, IVC, and aorta. The splenic vein courses posterior to the pancreas. The pancreas may be divided into the uncinate process, a small portion of pancreas that curls behind the SMV. The head of the pancreas is the thickest portion and wraps anteriorly around the SMV. The neck is the thinnest portion and lies just anterior to the SMV, the body lies in the midline and the pancreas usually tapers in the tail which extends superolaterally into the splenic hilum. If the left kidney is absent the pancreas and bowel may fall into the left renal fossa. Splenic artery calcifications seen in patients with atherosclerosis may mimic pancreatic calcifications or masses. Aneurysms of the splenic artery may also appear as pseudomasses. The pancreas is homogenous in appearance with attenuation similar to liver on unenhanced CT and following administration of contrast demonstrates homogenous enhancement with early brisk enhancement in the arterial phase and homogenous but slightly less enhancement on the portal venous phase. In older patients or in the setting of pancreatic atrophy due to other etiologies, it may develop a more feathery appearance because of fatty infiltration. The pancreatic duct should be small in caliber less than 3 mm, dilatation may indicate obstruction due to benign or

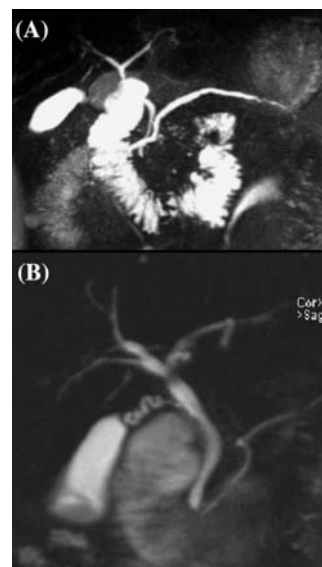


Figure 35 3D MR cholangiopancreatograms in two different patients demonstrate (A) a pancreas divisum where the main pancreatic duct drains through the dorsal pancreatic duct into the minor papilla compared with normal pancreatic anatomy (B) where the main pancreatic duct, representing the fusion of the ventral and dorsal ducts, drains into the major papilla. *Abbreviation:* MR, magnetic resonance.

malignant structure. The main pancreatic duct represents fusion of the dorsal and ventral ducts, which empty into the major papilla. The dorsal duct may also persist and drain separately from the main pancreatic duct via the minor papilla or the main pancreatic duct may completely drain through the dorsal pancreatic duct into the minor papilla known as pancreas divisum. The minor papilla or duct of Santorini enters the duodenum proximal to the major papilla or duct of Wirsung (Fig. 35). On FDG PET, minimal physiologic uptake is identified in pancreas.

Pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas that may either be diffuse or focal and may involve the adjacent retroperitoneal tissues as well as other adjacent organs. The most common causes are alcohol abuse and gallbladder disease. Other causes include drugs and other toxins, metabolic abnormalities such as hypercalcemia, infection, and vascular insult. The severity, chronicity, and complications will affect the appearance on pancreatitis on CT. Dynamic contrast-enhanced CT and MRI are most helpful at determining the presence and extent of necrosis, which impact prognosis. There is a staging system for acute pancreatitis, which is beyond the scope of this chapter (204). CT features on unenhanced imaging include enlargement,

heterogeneity of parenchyma, peripancreatic fat stranding and haziness, with peripancreatic fluid collections seen in more severe disease. Hemorrhage and fat necrosis may be manifested by increased density. Infection may occur with development of air-containing collections (205). Enhanced CT may reveal focal or diffuse decreased enhancement related to ischemia or nonenhancement secondary to necrosis, which may have more fluid density because of liquefaction. Rim-enhancing collections may develop, such as pseudocysts or infected pseudocysts or abscesses. More confluent enhancement may occur with phlegmonous collections. Inflammation related to pancreatitis begins in the peripancreatic region but may involve the retroperitoneal structures with inflammation tracking along the psoas muscles into the pelvis, perirenal spaces, or paracolic gutters.

In cases of pancreatitis, the pattern of increased FDG activity may be diffuse or focal in nature, and may be difficult to distinguish from malignancy, especially when inflammation is focal or mass-like (206–214). SUV is not sufficient to distinguish between benign and malignant processes (207,208,210,211,213,215,216). One report suggests that delayed imaging may differentiate between inflammation and malignancy (217) and another from the same group has suggested that kinetic analysis may help in distinguishing the two entities (218).

Autoimmune pancreatitis

Autoimmune pancreatitis (AIP), also known as primary sclerosing pancreatitis or lymphoplasmacytic sclerosing pancreatitis, is important to recognize because it has certain distinct imaging features and is managed differently than other types of pancreatitis. This form of pancreatitis responds to steroid therapy. This entity may occur in association with other autoimmune diseases such as Sjogren syndrome, primary sclerosing cholangitis, UC, and collagen vascular disease, and may be accompanied by retroperitoneal fibrosis (219). Imaging features include focal or diffuse (sausage-shaped) enlargement of the pancreas, pancreatic duct irregularity, homogenous but delayed enhancement, and a low attenuation rim surrounding the pancreas on contrast-enhanced CT (Fig. 36) (220,221). Additional extrapancreatic manifestations of AIP that can confound diagnosis include extra pancreatic biliary stenosis, enlarged salivary glands (Sjogren's), abdominal and cervical lymphadenopathy, retroperitoneal fibrosis, stenosis of the peripancreatic arteries and veins, and renal involvement (222,223).

The diffuse form may be difficult to distinguish from lymphoma, diffuse infiltrating adenocarcinoma, or metastases. With pancreatitis, there should not be vessel encasement by soft tissue or vascular invasion, unlike lymphoma

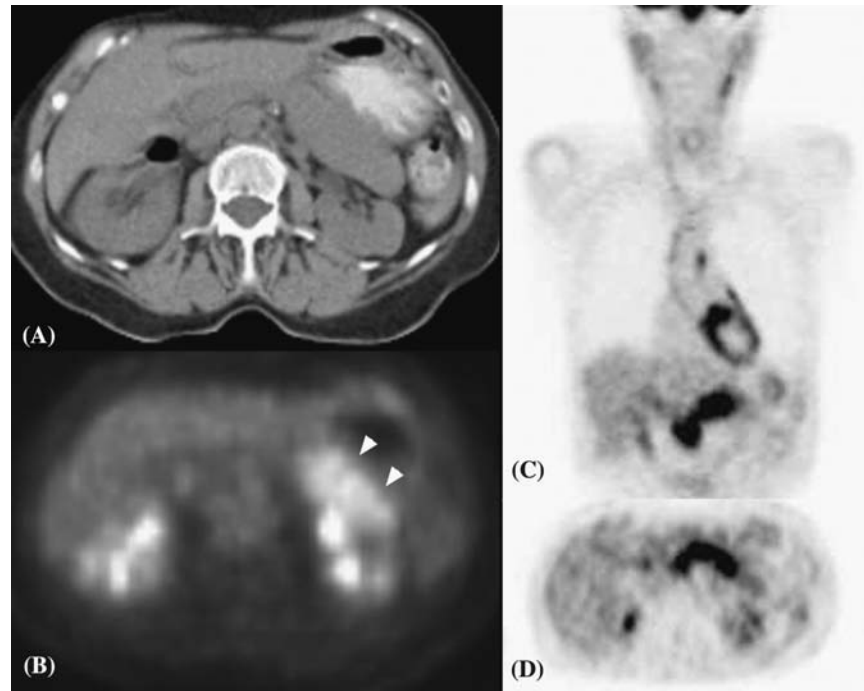


Figure 36 (A–B) PET/CT performed in a patient with focal autoimmune pancreatitis. (A) Unenhanced CT scan shows enlargement of the body and tail of the pancreas. (B) On the corresponding PET image, there is increased metabolic activity corresponding to the edematous pancreas (arrowheads). In another patient with autoimmune pancreatitis, (C–D) coronal (C) and transaxial (D) FDG PET images show diffusely increased uptake in the head, neck, and body of the pancreas. *Abbreviations:* PET/CT, positron emission tomography/computed tomography.

or adenocarcinoma, respectively. FDG PET will usually show diffuse uptake in active AIP but focal uptake has also been described (209,211,219,224). FDG accumulation in the inflamed pancreas will decrease with response to steroids (219) and provides a good analog of disease activity (209) (Fig. 36).

Chronic pancreatitis

Chronic pancreatitis leads to pancreatic atrophy with or without calcification. There may be pancreatic duct irregularity and beading with alternating focal areas of dilatation and stricturing without obstructing mass. Chronic pancreatitis may be focal and may mimic a mass that is isoattenuating to the remainder of the gland on enhanced and unenhanced CT such that biopsy may be warranted. FDG PET may show intense focal uptake in focal chronic pancreatitis (207,208,215).

Complications of pancreatitis

Complications of pancreatitis may be vascular such as splenic vein thrombosis leading to development of isolated perigastric varices and splenomegaly, splenic, or gastroduodenal artery aneurysms. Pseudocysts may develop, but usually not until four weeks after the initial episode. Pseudocysts may be seen as simple unilocular cyst with a thick rim, which may enhance or be more complex with septations and have a thick but smooth enhancing wall. Debris may be present with variably density. If gas bubbles are present, superimposed infection must be suspected unless there was recent surgical intervention. Pseudocysts are usually located within or around

the pancreas but may be located anywhere in the abdomen, pelvis, and even the chest. Other complications include infection with peripancreatic fat, peripancreatic fluid collections, necrosis, and abscesses.

Pancreatic Malignancy

Pancreatic adenocarcinoma

CT appearance of pancreatic adenocarcinoma is variable. On unenhanced CT, adenocarcinoma is usually isoattenuating relative to normal pancreas unless there is necrosis or cystic components, which demonstrate low attenuation foci (Fig. 37). Dynamic contrast-enhanced imaging is helpful for diagnosis and staging of pancreatic neoplasms. Venous phases are most useful where adenocarcinoma generally appears hypoattenuating relative to normal pancreatic parenchyma. IV contrast also permits visualization of the surrounding vasculature. The relationship of the tumor to the surrounding vessels indicates resectability. Greater than 50% encasement of the artery is considered suggestive of nonresectability as is encasement of the vein, distortion of its morphology, obliteration, and/or thrombosis. Secondary signs of malignancy that may be apparent include pancreas and biliary duct dilatation or a “double duct sign” with nontender distention of the gallbladder known as Courvoisier’s sign secondary to an obstructing pancreatic head neoplasm. Metastases may be seen in the liver, regional lymph nodes, adjacent retroperitoneal structures, and lung (Fig. 38). Periapillary carcinoma occurs within 2 cm of the major papilla and may look similar to pancreatic adenocarcinoma. Although treatment is similar, prognosis is more

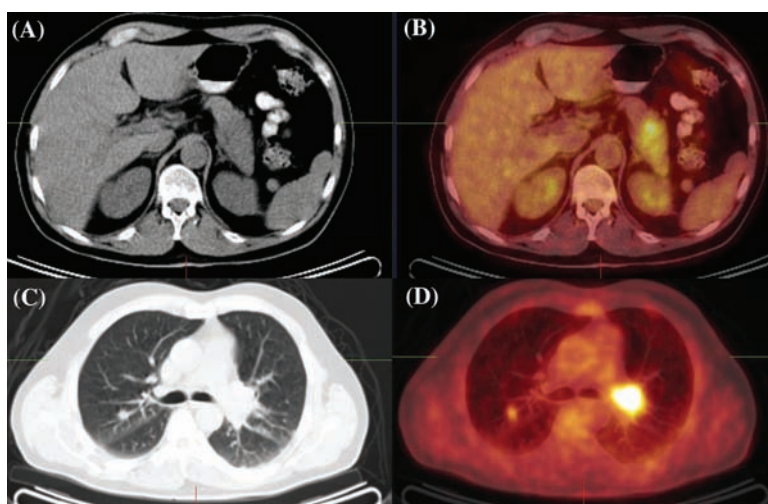


Figure 37 (A) Unenhanced CT from a PET/CT shows enlargement of the tail of the pancreas but no discrete mass. On the fused PET/CT image (B), this abnormality corresponds to a hypermetabolic focus. CT of the chest in this patient shows a large left hilar mass (C), which on the fused image (D) is also hypermetabolic representing metastatic lymphadenopathy. A hypermetabolic right upper lobe metastasis is also present (C). *Abbreviation:* PET/CT, positron emission tomography/computed tomography.

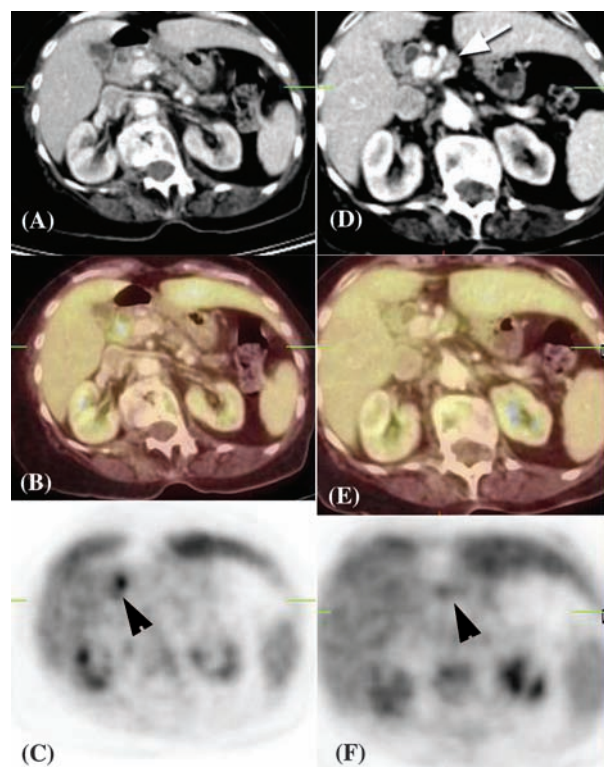


Figure 38 PET/CT performed in a patient with recently diagnosed primary pancreatic cancer for staging. (A) IV contrast-enhanced CT shows the dilated duct in the head of the pancreas just proximal to a small area of soft tissue density in the head of the pancreas shown on the fused image (B) and FDG PET slice (C). Just superior to this mass, a lymph node is noted (D) adjacent to the hepatic artery (arrow) which is also mildly hypermetabolic on the fused (E) and FDG PET (F) images. *Abbreviation:* PET/CT, positron emission tomography/computed tomography.

favorable. These tumors may bulge into the duodenal lumen and cause pancreatic and biliary obstruction.

CT and MRI are used primarily to image pancreatic ductal adenocarcinoma, but may be limited in the setting of enlargement of the pancreatic head without discrete mass, in mass forming pancreatitis (see pancreatitis above), in diagnosis of small locoregional lymph nodes, or in the detection of distant metastases. Metabolic imaging may be applied to improve preoperative diagnostic accuracy and potentially limit adverse outcomes from inappropriate surgical interventions (207,208,215). Although some studies have demonstrated the relatively high sensitivity and specificity of PET in distinguishing benign and malignant lesions in the pancreas, 92% and 85% in comparison with 65% and 62% for CT (215) and in another series a sensitivity of 98% and specificity of 94% (225), most authors find a significant overlap in the appearance of pancreatitis and pancreatic adenocarcinoma

on FDG PET (206–214). Nonetheless, the negative predictive value of PET is high except when glucose is elevated (225). PET is also less dependent on lesion size for diagnostic accuracy (226).

Cystic neoplasm

Pseudocysts are the most common cystic lesions of the pancreas and must be considered in the differential of cystic neoplasm. Another pitfall includes a duodenal diverticulum that can mimic a pancreatic head neoplasm (227) if filled only with fluid. Air within a diverticulum helps with differentiation from cystic neoplasm or pseudocyst. Neuroendocrine tumors and adenocarcinomas may appear cystic as well. On PET/CT, the primary challenge faced in the imaging of pancreatic cancer pertains to altered glucose metabolism created by glucose intolerance and diabetes seen in these patients. This setting may create false negative findings in patients who are hyperglycemic or have inadequately controlled blood glucose levels (225). False negatives may also result when the tumor is less than 1 cm, such as in small ampullary carcinomas and in mucinous carcinomas. For optimal evaluation of the pancreas on PET/CT adequate oral and IV contrast for the CT and careful attention to blood glucose in these patients, who may be at risk for glucose abnormalities, is critical.

Mucinous macrocystic neoplasm

These tumors are more common in middle-aged and younger females and are typically located in the body and tail of the pancreas. They are multiloculated, larger (usually >2 cm), and fluid density with cystic components, which may be benign or malignant. Enhancing soft tissue nodularity favors malignant etiology. Peripheral or septal calcification may be present. Occasionally, they can be unilocular making them difficult to differentiate from pseudocysts or serous cystadenomas.

Intraductal papillary mucinous neoplasms are more common in men and may involve a pancreatic side branch of the main duct. Main duct involvement leads to dilatation of the duct itself and is more often associated with malignant tumors. Soft tissue nodular components or papillary excrescences are also more suspicious for malignancy. They may be unilocular or contain grapelike clusters of cysts with internal septations and occasionally contain calcifications. FDG PET has been reported positive in these tumors (210,211).

Serous microcystic neoplasm

These lesions are more common in older females, more often located in the head of the pancreas and are usually benign. They are usually composed of small cysts less than 2 cm in size and may be water, soft tissue density, or heterogenous, but may be comprised of larger cysts mimicking mucinous neoplasms. Characteristic features

include enhancing septations yielding a stellate or honeycomb appearance more apparent in the venous or delayed phase of imaging, and central calcification.

Staging of pancreatic carcinomas

Tumor staging is primarily determined by anatomic imaging techniques, as it depends upon the relationship between the tumor, vascular structure, and adjacent organs. FDG PET is not clearly superior to CT for N staging, likely due to the proximity of lymph nodes to the primary mass, which may become obscured. However, in the case of anatomically small lymph nodes (<1 cm), with increased metabolic activity, PET/CT would have an advantage. PET/CT is more accurate than CT alone in the detection of distant metastatic disease. In studies, PET has demonstrated previously unsuspected metastases to the liver as well as in distant sites (Fig. 37). In the instance where neither PET nor CT showed metastatic involvement, intraoperative findings demonstrated carcinomatosis (215). Overall, PET/CT is a critical preoperative staging imaging modality for resection of pancreatic cancer, as it significantly improves patient selection and is ultimately cost-effective (228).

Monitoring response to treatment and detection of recurrence

Although large-scale studies have not been completed to date, preliminary work suggests the utility of PET/CT in determining response to neoadjuvant therapy and in predicting outcomes (229). One such pilot study suggested that the absence of FDG activity one month following the completion of chemotherapy is an indicator of potentially improved survival in contradistinction to those with persistent uptake (229). In terms of detection of recurrence, PET again demonstrates its ability to identify malignant foci before significant structural growth is detectable. Studies have shown up to 50% incremental information provided by PET, which resulted in alteration in the patient management plan (230).

Neuroendocrine or islet cell tumors

The majority of these lesions are functional and most often represent insulinoma or gastrinoma. They occur in and around the pancreatic head including the wall of the duodenum and stomach and may be multiple. Nonfunctioning islet cell tumors are more likely to be malignant. They can be seen in association with von Hippel Lindau syndrome and in patients with Multiple Endocrine Neoplasia type I. On unenhanced CT, the lesions are isointense relative to pancreatic parenchyma, but may contain calcification. Dynamic enhanced CT is warranted for visualization of these tumors because they are typically hypervascular or hyperdense compared with normal parenchyma on the arterial phase and iso- to hyperattenuating on the venous phase. Oral water contrast is useful to distend the duode-

num and better visualize small tumors. Small neuroendocrine tumors may mimic adenocarcinoma but are more likely to contain calcium and are less likely to be cystic or encase adjacent vessels than adenocarcinoma. The performance of FDG PET in the evaluation of neuroendocrine tumors of the pancreas has been mixed (231,232). In part, small size of the tumors at presentation is a limitation (231). In one series there was a sensitivity of only 53% (231). However, FDG PET has been used to follow the response of liver metastases from islet cell tumors (233).

Lymphoma

Lymphoma can involve the pancreas itself or peripancreatic lymph nodes. Lymphoma of the pancreas is usually associated with more systemic lymphadenopathy and is usually homogenous in appearance with vascular encasement but without invasion. FDG PET will predictably show increased uptake in non-Hodgkin's lymphoma of the pancreas (234).

Solid pseudopapillary tumors

Solid pseudopapillary tumors are rare, low-grade malignant tumors that occur in young women. They usually present as large tumors located in the tail, may reveal hemorrhage with fluid-fluid levels on fast spin-echo T₂-weighted MR images and demonstrate cystic degeneration. On contrast-enhanced CT, there may be peripheral enhancement that progressively fills in.

Metastases to the pancreas

Metastases to the pancreas are typically from melanoma, breast, lung, and renal cancer. They usually present as multiple solid masses and vary in appearance but are typically hypoattenuating. Melanoma and renal cancer may be hyperattenuating on early phase imaging because of hypervascularity. FDG uptake may be predicted by the avidity of the primary tumor for the tracer.

Postsurgical changes in the pancreas

Sphincterotomy to relieve biliary obstruction may lead to pneumobilia or low attenuating gas within the biliary tree. Alternatively, if there has been no recent intervention, pneumobilia may indicate more serious diseases such as infection or a biliary enteric fistula. Pancreatic head resection is usually performed as part of the Whipple procedure. The Whipple procedure includes a distal gastrectomy, duodenectomy, and removal of a portion of the pancreas. The jejunum is then anastomosed to the pancreas, biliary tree, and stomach. Choledochojejunostomy may lead to reflux of contrast material and air in the biliary tree. The pancreatic remnant may become atrophic and demonstrate pancreatic duct dilatation and there may be reactive lymphadenopathy or fat stranding which can simulate recurrence.

Isolated pancreatic tail resection may be performed and may include resection of the spleen. Central pancreatectomy may be performed for small low-grade tumors. Enucleation may be performed for small neuroendocrine tumors.

Gallbladder and Biliary Tree

Normal Anatomy

The normal gallbladder measures near water density and may demonstrate varying degrees of distention. The wall should be thin (<3mm) and will demonstrate smooth homogenous enhancement. The cystic duct is difficult to see unless dilated.

The right and left intrahepatic ducts are normally less than 2 mm in diameter and lie anterior to the portal vein. They join to form the common hepatic duct (CHD). The cystic duct drains into the CHD and forms the CBD. The CBD tapers normally and joins the pancreatic duct in the head of pancreas and drains into the duodenum via the ampulla of Vater or major papilla. The CBD and pancreatic duct may also drain separately into the ampulla. The intrahepatic ducts are fluid density structures that are not well seen on CT unless there is dilatation. The CBD normally measures less than 0.6 cm but may be slightly larger in diameter following cholecystectomy or may slightly dilate with age, but masses or obstructing stones should be excluded in the presence of dilatation.

Metallic and plastic stents may be placed in the CBD while other plastic stents may be placed in the pancreatic duct, and appear high density on unenhanced or even enhanced on CT. Stent complications include obstruction due to debris, stent migration, or tumor ingrowth.

Minimal physiologic FDG activity is seen in the gallbladder or biliary tract and these structures are usually indistinguishable from the liver. If the gallbladder, however, is distended, the lumen may appear photopenic on PET/CT scan.

Gallstones

Gallstones may be hyperdense if they contain calcium. Stones may also appear low density depending on the composition. Even gas and fat content may be seen within gallstones. Many stones are not radiopaque and will be missed on CT. Sludge may appear slightly hyperdense in comparison to biliary fluid and also may layer. This should not be confused with vicarious excretion of IV contrast agents through the biliary system, which can manifest a high-density material within the gallbladder on imaging. Polyps are soft tissue-enhancing masses in the wall of the gallbladder and may be confused with adherent stones. If less than a centimeter in size, they may be followed with serial US for interval growth, but the incidence of malignancy is low. Larger polyps (>1 cm) are suspicious for malignancy. Assessment of gallstones, polyps, and other disease processes such as adenomyomatosis and cholecystitis would be better assessed by ultrasound or MRI, but are often incidental findings on PET/CT.

Wall calcifications, also known as porcelain gallbladder, may be seen in the gallbladder, which carries an increased risk of gallbladder cancer.

Cholecystitis

Cholecystitis may be acute or chronic, and is most often associated with gallstones although acalculus cholecystitis may occur in the setting of diabetes, trauma, or as a consequence of parental nutrition. Rarely, in diabetics, emphysematous cholecystitis may be seen with gas in the wall of the gallbladder. Chronic inflammation may be mistaken for neoplasm. CT signs of cholecystitis include gallbladder distention, wall thickening, pericholecystic fluid, and pericholecystic fat stranding. Enhancement in the liver adjacent to the gallbladder fossa on early phase imaging may be seen secondary to per-cholecystic inflammation. Ultrasound and hepatobiliary scans are most sensitive for diagnosis in the presence of clinical symptoms. FDG uptake may be seen in the wall of the gallbladder in acute cholecystitis (Fig. 39) (235,236), TB (237), and less

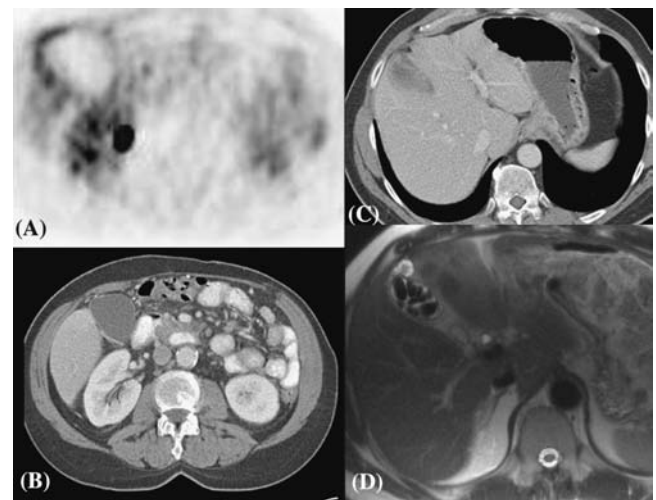


Figure 39 (A) FDG PET performed in a patient with pancreatic cancer demonstrates ring-like increased metabolic activity corresponding to the gallbladder wall on the corresponding CT image (B). In another patient, the CT image (C) fails to demonstrate gallstones but does demonstrate nonspecific wall thickening at the fundus typical of adenomyomatosis. This is not specific and can mimic carcinoma. On the corresponding MRI slice, the “pearl necklace” sign of fundal adenomyomatosis and gallstones are seen on T2-weighted MRI (D). *Abbreviations:* PET, positron emission tomography; CT, computed tomography; MRI, Magnetic resonance imaging.

consistently so in chronic cholecystitis (238–240). Gallbladder wall thickening and wall edema can be seen in acute or chronic cholecystitis, hepatitis, portal venous hypertension, congestive heart failure, hypoalbuminemia, adenomyomatosis, AIDS, and gallbladder carcinoma.

Adenomyomatosis

Adenomyomatosis is a benign condition in which there is thickening of the muscularis of the gallbladder wall and mucosal proliferation. It may be focal or diffuse and most commonly affects the fundus. On CT, adenomyomatosis appears as focal or diffuse wall thickening. However, it is better characterized by MRI or ultrasound. On MRI, the dilated Rokitansky–Aschoff sinuses; or mucosal protrusions into the muscle wall, are seen as T2 hyperintense foci with variable signal on T1. These sinuses may cause “comet tail” artifact on US. On CT, adenomyomatosis may mimic gallbladder cancer because of the apparent wall thickening. FDG uptake has been reported in association with adenomyomatosis (237) (Fig. 39).

Choledocholithiasis

Choledocholithiasis may cause obstructive jaundice. On CT, stones may be hyperdense and visible within the lumen of the CBD with or without associated biliary duct dilatation. More often, stones are nonradiopaque and similar in density to fluid within the CBD. Positive or hyperattenuating oral contrast may obscure distal CBD stones. If there is unexplained biliary duct dilatation, MR cholangiopancreatography or endoscopic retrograde cholangiopancreatography (ERCP) may be helpful.

Pneumobilia is discussed above and may be iatrogenic introduced as a result of intervention such as sphincterotomy, ERCP, or surgical biliary enteric anastomosis. On the other hand, it may be a sign of infection or a biliary enteric fistula caused by peptic ulcer disease or erosion from chronic inflammation due to gallstones.

Cholangitis

Cholangitis refers to infection in the biliary tree usually bacterial or parasitic in etiology and typically due to obstruction. CT findings include biliary duct dilatation with periductal enhancement and gallbladder wall thickening (Fig. 40).

Recurrent pyogenic cholangitis is a result of clonorchis sinensis ascaris with bacterial superinfection and is endemic to Southeast Asia. Biliary duct dilatation, structure, and noncalcified calculi are usually present. Pigmented calculi seen in this disease process may have soft tissue density, but should not enhance. Complications include abscess, portal vein occlusion, cholangiocarcinoma, pancreatic duct, or gallbladder involvement.

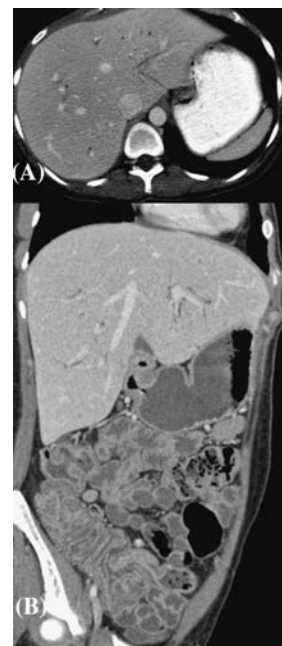


Figure 40 Patient with ulcerative colitis and primary sclerosing cholangitis. Axial (A) and coronal reformatted (B) CT scans show the irregular biliary ductal dilatation associated with primary sclerosing cholangitis and the mild colonic wall thickening related to the patient's known ulcerative colitis. *Abbreviation:* CT, computed tomography.

PSC is a chronic inflammatory disease, which may be idiopathic or secondary to inflammatory bowel disease, more often UC, pancreatitis, retroperitoneal fibrosis, hepatitis, and cirrhosis. Males are more commonly affected. CT features include irregular beading of the biliary tree with alternating areas of narrowing and dilatation associated with periductal enhancement, which varies in degree depending on severity of disease and phase of contrast enhancement. It has been associated with FDG uptake in isolated reports (241). Complications include cirrhosis, portal hypertension, and cholangiocarcinoma.

Cholangiocarcinoma

Cholangiocarcinoma should be suspected in the absence of a mass if there is focal eccentric periductal wall thickening. Extrahepatic cholangiocarcinoma may also present as a high attenuating mass with thickening of the bile duct wall causing obstruction. Dynamic contrast-enhanced MRCP may be helpful for further assessment to reveal subtle changes of PSC and to detect and stage extent of cholangiocarcinoma (242). On MRI, bile duct wall thickening of greater than 5 mm is considered suspicious for malignancy (243). However, this is not always reliable such that authors suggests that high grade obstruction disproportionate to the degree of wall thickening may be a more helpful

indicator of malignancy on MRI (244). On both CT and MRI, 5- to 10-minute delayed imaging following administration of contrast may reveal the underlying tumor as it may continue to enhance and become more hyperattenuating relative to surrounding liver parenchyma, probably because of the fibrosis associated with these lesions.

Overall sensitivity and specificity of PET for cholangiocarcinoma of 61% and 80%, respectively, have been reported (245) (Fig. 41). More recently, a sensitivity of either PET or PET/CT for recurrent or metastatic cholangiocarcinoma of 94% compared with 82% sensitivity with CT alone and a specificity of 100% for PET or PET/CT compared with 43% with CT alone has been identified (203). Further evaluation based on morphology increased the sensitivity to 85% by analyzing only patients with nodular type tumors. Conversely, sensitivity for infiltrating cholangiocarcinoma was lower (203,245). In sclerosing

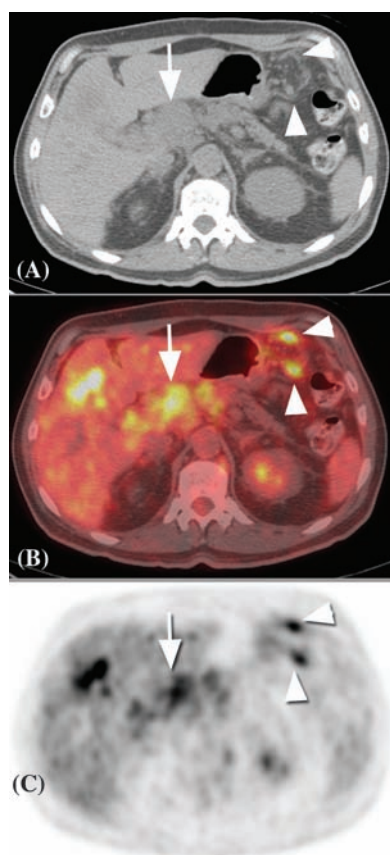


Figure 41 (A) unenhanced CT, (B) fused PET/CT, and (C) corresponding PET image show the increased metabolic activity of the mass (arrows) at the porta hepatis representing the primary cholangiocarcinoma in this patient. Also seen are a liver metastasis and small mesenteric implants in the left upper quadrant (arrowheads) best seen on fused imaging. *Abbreviations:* CT, computed tomography; PET, positron emission tomography.

cholangitis, the sensitivity was 100% and the specificity was 80%, with a false positive secondary to acute cholangitis, but sensitivity may be less for smaller early tumors (200). Inflammation from biliary stents may present interpretation challenges, but use of the concomitant CT aids in appropriate diagnosis. Sensitivity for metastatic disease was 65%, with false negatives related to less than 1 cm intraperitoneal lesions (245).

Adenocarcinoma of the Gallbladder

Adenocarcinoma has a predilection for older, female patients. Cholelithiasis, porcelain gallbladder, PSC, and congenital anomalies are all predisposing risk factors. They more commonly arise in the fundus and can be mistaken for adenomyomatosis. Adenocarcinoma of the gallbladder may be focal or infiltrative and diffuse. CT may demonstrate focal or diffuse wall thickening with irregularity or focal mass and may directly invade the liver. It has been suggested that FDG PET may be helpful to differentiate between benign and malignant gall bladder wall thickening, although false positives occur (240,241). Lymphadenopathy due to metastatic disease may be present, but chronic inflammation may also lead to lymphadenopathy. Ill-defined gallbladder wall enhancement help distinguish malignancy from cholecystitis, which will more likely demonstrate smooth wall enhancement.

Since most patients are diagnosed with gallbladder carcinoma after cholecystectomy, the utility of PET/CT is primarily in the initial staging or in restaging when recurrence is suspected (246). Relative sensitivity and specificity for residual gallbladder carcinoma with FDG PET was 78% and 80%, respectively (245). Sensitivity for distant metastases was only 56%, and although PET detected laparoscopic port-site recurrence, it was limited, again, in its ability to identify carcinomatosis.

Metastatic disease to the gallbladder is most commonly due to melanoma or breast cancer.

Adrenals

Normal Anatomy

The adrenal glands lie in the perirenal fat. The right adrenal gland is located posterior to the IVC between the right crus of the diaphragm and the liver. Masses arising from the adrenal gland may displace the IVC anteriorly and the kidney inferiorly. The left adrenal lies medial and anterior to the upper pole of the left kidney. They may be “v” shaped or triangular. They each have a medial and a lateral limb that converge anteriorly at the apex. They are smooth and symmetric in thickness and uniform in density. Adjacent structures may mimic adrenal masses including gastric fundal diverticula, varices, exophytic renal masses, and retroperitoneal lymphadenopathy. If there is congenital

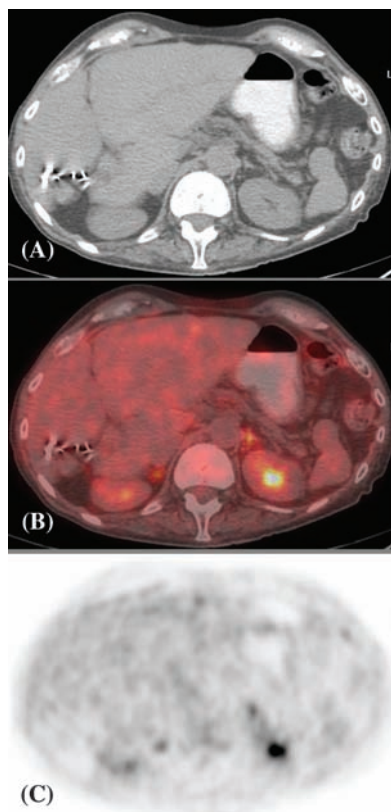


Figure 42 PET/CT was performed in this patient with a history of metastatic colon cancer previously treated with resection and partial hepatectomy. The left adrenal appeared normal on CT (A), but uptake in the adrenal gland on (B) fused images and PET alone (C) was relatively intense (SUV 3.4). The patient had Addison's disease and there was no change in the adrenal gland on either CT or PET on follow-up. *Abbreviations:* CT, computed tomography; PET, positron emission tomography; SUV, standardized uptake value.

absence of the kidney, the ipsilateral adrenal may appear linear rather than have its usual triangular or "v" shape.

No increased FDG uptake is usually seen in the adrenal glands. At times, there may be unilateral or bilateral diffusely increased activity, which may be physiologic in nature, and likely secondary to the functioning adrenal gland. This has been seen in Addison's disease as well (Fig. 42).

CT Imaging Tips and Techniques for the Adrenals

Small adrenal masses may not be visualized or be adequately characterized if collimation is too thick. Thin section images approximately less than 50% of the lesion size are required to enable characterization. Multiplanar reconstructions may be helpful to differentiate an adrenal

mass from a renal mass, e.g., or adrenal masses from pseudotumors such as gastric diverticuli or varices.

Benign Neoplasms

Because of the widespread use of cross-sectional imaging, and PET/CT is no exception, many small indeterminate adrenal lesions are discovered incidentally. If there is no history of a primary malignancy, the vast majority of these lesions are benign, nonfunctioning adenomas. Even in a patient with a primary neoplasm, most adrenal masses are still benign (247). However, it is important to distinguish between lesions that require intervention and lesions that can be monitored.

Adenomas

Adenomas are often incidentally found and asymptomatic. Hyperfunctioning adenomas cannot be specifically diagnosed by any imaging modality; clinical history, or laboratory data, and possibly adrenal venous sampling may be required. Noncontrast CT imaging is useful because if a less than 3 cm mass is found that measures <10 HU, then it is considered an adrenal cortical adenoma. Large (>3 cm) masses may still be adenomas but if a lesion is larger than 6 cm, it should be closely followed, biopsied, or even removed as malignancy cannot be entirely excluded. Lesions between 4–6 cm may also require close follow up. If the lesion remains indeterminate and there is clinical concern for malignancy, then additional imaging may be warranted. Alternatively, more conservative management including a detailed clinical history and endocrine evaluation along with imaging follow up in three to six months may suffice. Thirty percent of adenomas are lipid-poor, meaning they do not meet unenhanced CT criteria for adenoma. The next imaging options include unenhanced chemical shift MRI to look for even a small amount of fat within the lesion. Adenomas may be so lipid-poor, however, that this is not helpful, and they may be difficult to differentiate from a solid neoplasm. Contrast-enhanced CT with early and/or delayed imaging at 10 minutes has been found to be very useful for characterizing adrenal adenomas. If the lesion is less than 35 HU on delayed imaging or there is greater than 50% washout between early 60- and 90-second and 10-minute delayed imaging, it is most likely an adenoma (248,249). If not, biopsy or close follow-up may be warranted. Prior imaging is very important, as well, to assess for interval change. In patients with underlying malignancy a newly identified lesion would be suggestive of malignancy unless there had been recent intervention or trauma that would raise the possibility of hemorrhage. Hemorrhage is typically high density on unenhanced CT between 50 and 80 HU, and should not enhance. MRI with and without IV gadolinium chelate contrast can be helpful in differentiating hemorrhage or hematoma from a soft

tissue mass. Additionally, postprocessing techniques such as subtraction may enable more confident detection of enhancement or the absence thereof. Very rarely, pheochromocytoma can mimic an adenoma such that clinical signs, symptoms, and laboratory data are required if a functioning lesion is suspected. It is important to remember that 20% of pheochromocytomas are asymptomatic; so one must always consider this diagnosis because missing it can cause serious complications.

Focally increased uptake may represent either adenoma or metastasis. Adrenal uptake, isointense or less intense than the liver, is more likely to be benign. Overall, a comparison of adrenal gland uptake to liver activity in lung cancer patients demonstrated a sensitivity of 93% and a specificity of 90% (250). In addition, the use of an SUV guideline of 3.1 in combination with concomitant CT data of HU less than 10, consistent with lipid containing adenomas, yielded a sensitivity and specificity of 100% and 98%, respectively (251) (Figure 43).

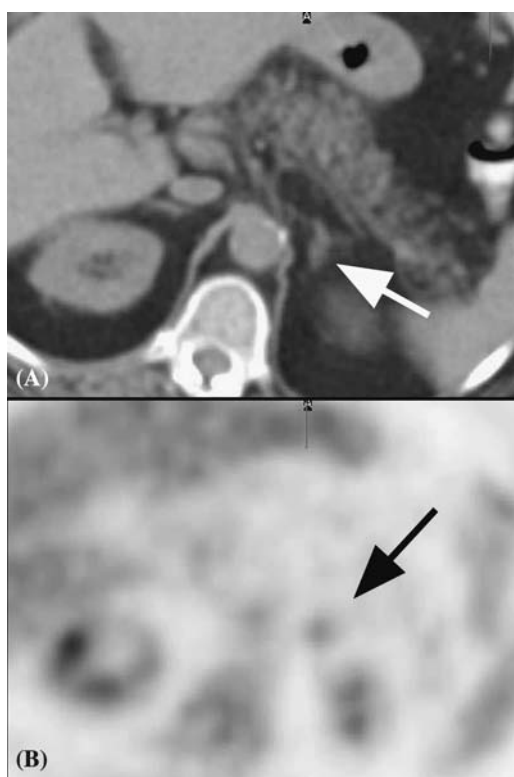


Figure 43 PET/CT performed for staging of non-small cell lung cancer shows minimal enlargement of the medial limb of the left adrenal gland (*arrow*) on unenhanced CT (A), which corresponds to the mildly increased metabolic activity (SUV 2.4) (*arrow*) (B). Although the density on CT is not highly suggestive of an adenoma, this remained stable over several repeat scans and was felt to be benign. *Abbreviations:* PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value.

Adrenal cortical hyperplasia

Hyperplasia may occur secondary to stress related to trauma or sepsis, Cushing syndrome resulting from overproduction of cortisol, other metabolic or hormonal disorders, and malignancy. Adrenal hyperplasia may cause diffuse smooth or nodular adrenal gland thickening and is typically bilateral and symmetric. The normal morphology of the adrenal gland should remain intact. While often asymptomatic, they too may be functioning. Attenuation remains similar to normal adrenal tissue.

Adrenal calcifications

Adrenal calcification may be rim-like in adrenal cysts and lymphangiomas. In the rare hemangioma rounded phleboliths will be present. Calcification may also be present as a sequela of hemorrhage, trauma, sepsis, coagulopathy, and infection particularly granulomatous disease. Benign and malignant neoplastic lesions such as myelolipomas, adrenal cortical carcinoma, or neuroblastoma may contain calcium as well. Metastatic lesions such as mucinous metastases from lung, melanoma, breast carcinoma, or sarcomas may calcify.

Adrenal hemorrhage

Adrenal hemorrhage may occur as a result of trauma, anticoagulation therapy, post surgery, or biopsy. Hemorrhage should not typically enhance and if enhancing soft tissue is present biopsy may be warranted. This can be assessed with unenhanced and enhanced CT or MRI. Chemical shift imaging may help identify hemorrhage or hemosiderin as well as detect subtle enhancement. FDG PET has been reported to be positive in adrenal hemorrhage (252).

Myelolipomas

Myelolipomas are benign nonfunctioning neoplasms composed of hematopoietic tissue and fat. They vary in size and may have necrosis or hemorrhage with punctate calcification seen in up to 20% of cases. CT imaging should reveal low attenuation, fat density elements. The lipid-poor type may require biopsy because they cannot be distinguished from other solid masses.

Adrenal cysts

Low density adrenal cystic lesions may represent cysts, but these are uncommon. Other cystic lesions include pseudocysts, epithelial cysts, and parasitic cysts. They may have septations and contain debris particularly pseudocysts. Rim calcification or smooth thin wall or septal enhancement may be present but no soft tissue nodular components should be present. These are predictably hypometabolic on FDG PET.

Other solid masses

Pheochromocytoma should be considered in the differential of any adrenal mass, and may be asymptomatic in 10% to 20% of cases. They are typically unilateral masses with about 90% within the adrenal gland and 98% within the abdomen. Extra-adrenal pheochromocytoma are commonly located in the organ of Zuckerkandl at the aortic bifurcation, bladder wall, or chest and are called paragangliomas. 10% are malignant, 10% hereditary, and up to 10% may be multiple or bilateral. Pheochromocytomas are associated with Von Hippel Lindau, neurofibromatosis, and MEN I syndrome. Calcification is uncommon and usually rim-like. Small lesions may be homogenous in appearance with soft tissue density but may undergo hemorrhage or necrosis and contain low attenuation components centrally. They tend to be very vascular and enhance heterogeneously following administration of contrast. Larger lesions may also show hemorrhage and rarely cystic changes mimicking other lesions. Infusion of iodinated contrast can cause elevation in catecholamines and precipitate a hypertensive attack such that patients should be closely monitored or premedicated with antihypertensives. Nuclear scintigraphy with meta-iodobenzylguanidine (MIBG) is useful for localization and octreotide may be used, as a small percentage of these tumors may be seen only on In-111 octreotide (253). MRI is useful because pheochromocytomas may be readily identified by their T2 characteristics and IV gadolinium chelate agents are less likely to precipitate a hypertensive crisis.

FDG PET has been found useful with a 100% per patient sensitivity and a 97% per body region sensitivity for pheochromocytomas, better than either CT or MRI in one series and particularly useful in identifying metastases (253) (Fig. 44). Interestingly, MIBG negative lesions tend to be positive with FDG (253) and FDG has been found to be more sensitive than MIBG especially after I-131 MIBG treatment (253–255) and in aggressive pheochromocytomas (256). Other PET tracers including 18F-fluorodopamine and 11C-metahydroxyephedrine have been used to image pheochromocytomas, but in general offer little advantage over FDG PET in terms of sensitivity (253,255).

Adrenal Cortical Carcinoma

Adrenal cortical carcinomas are very rare tumors that can produce endocrine-related symptoms. They usually present as large vascular neoplasms with heterogeneous enhancement. They have a tendency to invade the adrenal vein and the IVC, differentiating them from other adrenal neoplasms. Calcification may be seen in 20% to 30% cases. FDG PET will be positive in these tumors, but nonspecific (257), and may alter staging from conven-

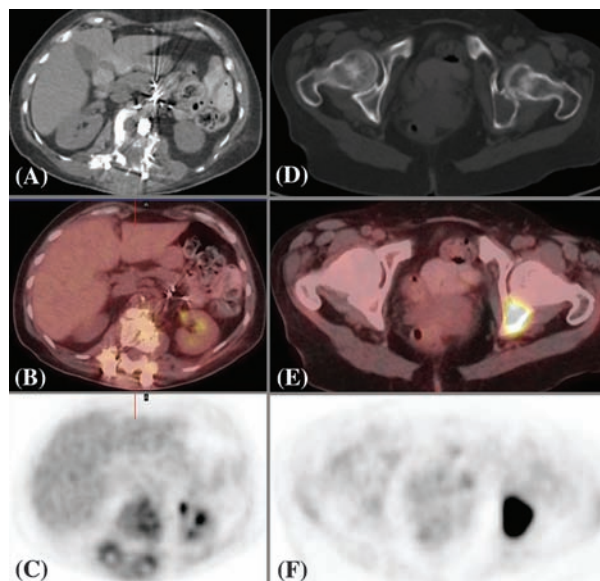


Figure 44 A 57-year-old woman with a history of a left adrenal pheochromocytoma and metastases to the spine, both of which were resected. The patient presented with newly increased metanephrines. Axial unenhanced CT (A), fused (B) and PET (C) images at the site of the original disease showed no evidence of recurrence. However, in the left acetabulum a lytic lesion on CT (D) is highly metabolic on fused (E) and PET (F) images. *Abbreviations:* CT, computed tomography; PET, positron emission tomography.

tional imaging (258). FDG PET has been effective at evaluating recurrences except with very small tumors (193) and can make a difference in management (258). No significant difference in sensitivity has been found between PET/CT (90%) and diagnostic CT (88%) for detecting recurrent adrenocortical carcinoma lesions overall, but PET/CT appears to be superior for detecting local recurrence (259). Furthermore, SUV appears to correlate with prognosis after recurrence (259). Experimental work with ^{11}C -metomidate has shown greater specificity, but only modest uptake in adrenal cortical malignancy (257,260).

Adrenal lymphoma

Lymphoma may be primary or secondary. Primary lymphoma may be unilateral and secondary lymphoma bilateral and may mimic infection with symmetrical enlargement. FDG PET will be positive but nonspecific (261–263) (see chap. 17).

Metastases

Metastases are found in about 25% of patients with underlying epithelial neoplasms. Most common etiologies include lung, breast, melanoma, renal cell carcinoma, thyroid, and gastrointestinal primary carcinomas.

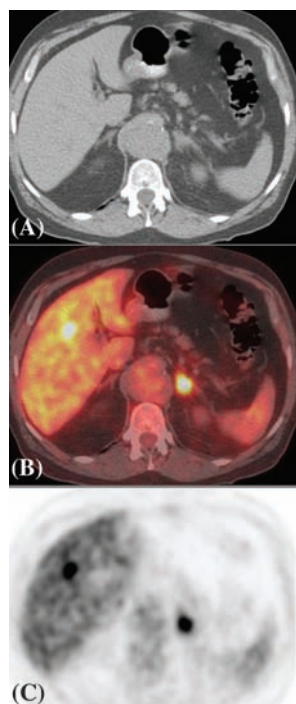


Figure 45 A 73-year-old man with non-small cell lung cancer. A PET/CT was performed because of suspicion of new metastatic disease. CT (A) shows an enlarged left adrenal gland of soft tissue. The fused PET/CT (B) and PET (C) show increased metabolic activity in this adrenal mass consistent with a metastasis. There is also a focus of increased activity in the liver in spite of the normal appearance of the liver on the unenhanced CT. *Abbreviations:* CT, computed tomography; PET, positron emission tomography.

Metastatic deposits may be unilateral or bilateral and vary in size and appearance. Calcification is rare and dependent on the primary tumor. Metastases may arise within adenomas known as collision tumors, and may be seen as areas of heterogeneity on unenhanced CT, but chemical shift MRI is more useful for identifying a nonfatty metastatic lesion within a lipid-rich adenoma. This is one of the most common causes of increased FDG uptake in the adrenal given the usual population of patients undergoing PET/CT (Fig. 45). FDG PET alone has shown high sensitivity and specificity for metastases in the setting of a known primary tumor and is particularly helpful when adrenal lesions are indeterminate on CT (264,265). A false positive rate of 16% in a patient population with known primaries has been reported (265). Although a cut-off of SUV 3.1 to 3.4 has been suggested as discriminatory between benign lesions and metastases, visual inspection is as effective (264). FDG uptake has been reported in metastases to the adrenal from a variety of primary tumors (Table 16). In a large series of patients with non-small cell

Table 16 Adrenal Metastases Reported on FDG PET

Author (Ref.)	Primary tumor
Kumar, 2004 (250)	Non-small cell lung cancer
Brink, 2004 (331)	Small cell lung cancer
Khan, 2006 (332)	Colorectal cancer
Seshadri, 2006 (333)	Melanoma
Iagaru, 2007 (334)	Anaplastic thyroid cancer
Kobayashi, 2006 (335)	Malignant fibrous histiocytoma
Mucha, 2006 (336)	Medullary thyroid cancer
Lim, 2006 (337)	Gastric cancer
Ide, 2005 (338)	Renal cell carcinoma
Watanabe, 2004 (99)	Duodenal cancer

lung cancer the accuracy in discriminating metastases from benign disease was 92% (250).

Spleen

Normal Anatomy

The spleen lies below the left hemidiaphragm within the left upper quadrant and is smooth in contour but can vary in size. Contour abnormalities such as clefts and lobulations are common and should not be confused with masses. Physiologic activity in the spleen should be homogeneous and less than that of the liver. In a recent study of patients with normal spleens, SUV ranged from 1.6 to 4.1 (266).

Accessory spleens are found in 1 in 10 people and appear as round masses isoattenuating to spleen on unenhanced and enhanced imaging. These splenules may be located near the splenic hilum. On PET/CT, these nodules will be seen to be hypometabolic or similar to the intensity of the normal spleen. Technetium sulfur colloid radionuclide studies may be helpful to confirm the presence of splenic tissue. Wandering spleen refers to normal spleen in an aberrant location. Splenosis or ectopic foci of spleen may occur as a result of trauma and can mimic peritoneal metastases but should not be hypermetabolic on PET.

Normally, the spleen should be <12 cm in craniocaudal dimension. Infection, inflammation, collagen vascular disease, portal hypertension, anemia, and neoplasm can all cause splenomegaly. In some of these entities, splenic uptake will be increased relative to liver (Table 17). In inflammation, this is likely due to activation of lymphocytes (267). In the setting of growth colony stimulating factor administration, diffusely increased radiopharmaceutical uptake in the spleen is nonspecific, and although is most likely secondary to effects of the drug, the possibility of underlying pathology cannot be completely excluded (Fig. 46).

Splenic enhancement patterns on CT are variable from a nodular pattern, to a striped or wave-like pattern, and may be mistaken for pathologic conditions. It is important

Table 17 Conditions Associated with Increased Splenic Uptake

Condition	Finding (Ref.)
Inflammation/Infection	
Sarcoidosis	Focal (339)
Hepatitis	Diffuse (171)
Malaria	Diffuse (340)
Infectious mononucleosis	Diffuse (341)
Metastases	
Hepatocellular carcinoma	Focal (276)
Non-small cell lung cancer	Focal (274)
Melanoma	Focal (275)
Lymphoma	
Hodgkin's disease	Diffuse or focal (271,342)
Non Hodgkin's lymphoma	Focal (271) or diffuse (343)
Other	
Colony stimulating factor administration	Diffuse (344,345)
Myelofibrosis	Diffuse (346)
Extramedullary hematopoiesis (chronic anemias)	Diffuse (347)

to remember that the vast majority of splenic lesions are benign. On CT imaging, there is significant overlap in appearance between benign and malignant splenic lesions, e.g., infection. Thus, correlation with a detailed clinical history and follow-up imaging may be warranted. MRI may be useful as an adjunct for further characterization of the indeterminate splenic mass. Many infections will manifest with diffusely increased splenic uptake.

Cystic Lesions

Splenic cysts include posttraumatic pseudocyst, echinococcal cysts due to infection, and congenital epithelial cysts, which are rare. Pseudocysts and echinococcal cysts are similar in appearance when they occur in the spleen, pancreas, or liver as described earlier in this chapter. These are typically hypoactive on PET if they are large enough to be resolved. Lymphangiomas may be variable in appearance but are typically septated cystic lesions and may be solitary or multiple and may contain thin rim or septal calcification. No enhancement is seen within these lesions except for possibly thin septal and wall enhancement.

Abscesses

Infection may lead to nonspecific splenic enlargement or focal abscesses usually manifested by multiple low attenuation lesions. They tend to be hypoattenuating relative to the spleen on unenhanced CT and may demonstrate rim enhancement following contrast administration with low attenuation centrally. Although splenic abscesses on FDG PET have not been reported specifically, they would be expected to be active. Miliary patterns may be seen with

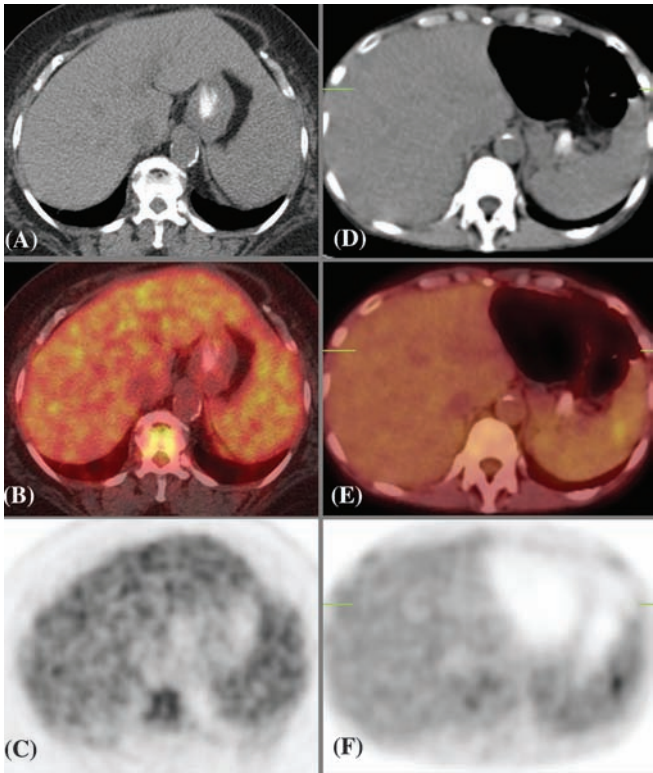


Figure 46 (A–C) PET/CT performed in a patient midway through chemotherapy for non-Hodgkin's lymphoma. The patient was receiving colony stimulating factors for marrow support. The PET (C) shows mildly and diffusely increased uptake in the spleen relative to the liver. (D–F) Another patient with Hodgkin's disease who presented for staging prior to therapy. The CT (D) of the spleen is normal, but on the fusion (E) and PET (F) images a focus of uptake is present in the spleen consistent with lymphoma. *Abbreviations:* PET, positron emission tomography; CT, computed tomography.

fungal infections but also with lymphoma. Calcification may be seen in treated candidiasis, histoplasmosis, mycobacteria, and pneumocystis carinii.

Infarcts

Splenic infarcts are seen as wedge shaped, hypoenhancing, and avascular regions with retained rim enhancement in the splenic capsule similar to the appearance of renal infarct.

Calcification

Focal or punctate calcification may be seen in hemangiomas, as a result of prior infection, especially granulomatous infections. Rim calcification can be seen in cysts related to infection or pseudocysts. The entire spleen may become infarcted, shrink, and calcify as seen in sickle cell disease.

Solid Lesions

Benign masses

Hemangiomas may appear similar to hemangiomas in the liver but are more likely to present atypically in the spleen. Prolonged enhancement similar to intensity of the aorta should be seen.

Hamartomas are rare lesions that may be solitary or multiple and are well circumscribed lesions variable in size that are typically hypodense to splenic tissue but may be isointense to spleen. Prolonged enhancement like hemangiomas may be present.

Littoral cell angiomas are benign lesions but have been reportedly associated with other malignancies such as colorectal, renal, pancreatic adenocarcinoma, and meningioma. These lesions are variable in size, multiple, and typically low attenuation but may demonstrate delayed enhancement and become isointense to spleen (268). However, the differential diagnosis is broad including primary tumors of the spleen, metastatic disease, infection, or inflammatory diseases such as sarcoidosis.

Sarcoid

Sarcoid in the spleen presents with splenomegaly and/or multiple low attenuation lesions similar in appearance to lymphoma. There may be concomitant liver involvement and lymphadenopathy. FDG uptake can be intense in active disease in the spleen (175). Chest CT may be warranted to look for signs of underlying sarcoidosis, and FDG PET likely will demonstrate extrasplenic uptake in a distribution suggestive of sarcoid or, at the very least identify, a site for biopsy (Fig. 47).

Lymphoma

Splenic involvement occurs in about one-fifth to one-quarter of patients with lymphoma (269,270). Primary splenic lymphoma is rare. Primary or secondary lymphoma may lead to splenomegaly. Focal lesions may be present, ranging from solitary to multiple masses variable in size, but typically with low attenuation on CT (Fig. 46). On PET, focal lesions will usually be hypermetabolic, but splenomegaly and diffusely increased uptake (greater than the liver) should also be considered signs of splenic involvement (271–273).

Metastases

Metastatic disease to the spleen is unusual but the most common etiologies include lung, melanoma, and breast cancer. These are active on FDG PET (274,275). Metastases from HCC have also been reported on PET (276) (Table 17). Hyperdensity due to hemorrhage may be associated with melanoma metastases. Other metastases tend to low attenuation on unenhanced CT. Following administration of contrast, they may demonstrate relatively

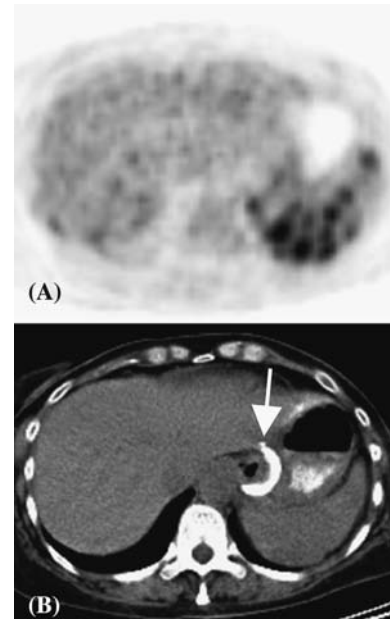


Figure 47 PET (A) and corresponding CT (B) performed in the 43-year-old woman who presented with diffuse lymphadenopathy. Multiple foci of uptake in the spleen, in spite of a relatively unremarkable appearance on unenhanced CT. Differential diagnosis includes lymphoma; however, biopsy of a supraclavicular lymph node revealed noncaseating granulomas consistent with sarcoidosis. Note the gastric band (B) near the gastroesophageal junction (arrow). *Abbreviations:* PET, positron emission tomography; CT, computed tomography.

low attenuation centrally and irregular rim enhancement. Cystic metastases may occur from ovarian and breast cancer. Capsular metastases may occur from peritoneal carcinomatosis (as in ovarian cancer) and are often exquisitely delineated on PET/CT or direct extension from pancreatic neoplasms.

Retroperitoneum

Although PET/CT is rarely performed for evaluation of the retroperitoneum, a basic understanding of the anatomy and some of the more common pathologic entities that occur here should be considered. The retroperitoneal space is bounded by the posterior aspect of the parietal peritoneum and psoas, quadratus lumborum, and transversalis musculature posterior and laterally. The retroperitoneal space surrounding the kidneys is separated into the anterior and posterior pararenal space, which is separated from the perirenal space by Gerota's fascia, which is a thin rim of tissue that can often be seen, particularly if surrounded by fluid. The anterior pararenal space includes the duodenum, pancreas, and ascending and descending colon. It is bounded anteriorly by the parietal peritoneum,

laterally by the lateral conal fascia, and posteriorly by the anterior renal fascia (277). Causes of fluid accumulations in the retroperitoneum include pancreatitis that may lead to either phlegmon or effusion.

Retroperitoneal hematomas will appear as a soft tissue density in the retroperitoneum displacing adjacent structures. In an acute bleed, the density will have a higher attenuation, but as the hematoma ages, the attenuation of the mass should decrease, as should its size. Retroperitoneal hematomas have been associated with ruptured or leaking aortic aneurysms (278), arterial punctures above the inguinal ligament (279), and blunt trauma, most commonly (278). Since their appearance is nonspecific, tumor, urinoma, lymphocele, and abscess must be excluded.

Abscesses will appear as a cavity, containing fluid and sometimes air (280). The source is usually from the gastrointestinal tract, the kidneys, the spine, or the iliopsoas muscle (280) and the etiology is often urolithiasis, appendicitis, urologic instrumentation or surgery, or unknown (281). While hematomas are generally not FDG avid, abscesses will accumulate FDG at least in their walls (282).

Vascular Structures

The caliber of the abdominal aorta is normally less than 3 cm. An aneurysm is defined as greater than or equal to 3 cm. The aorta may contain atherosclerosis, intramural hematomas, dissections, and ulcerations.

Aortitis will present with periaortic soft tissue and fat stranding. FDG uptake in the wall of the aorta is commonly seen in the presence of atherosclerosis and likely represents the inflammatory nature of the process. More intense uptake is seen in aortitis associated with autoimmune disease (283,284). While this is not an accepted application of PET, successful treatment with corticosteroids of aortitis will result in a reduction of FDG accumulation (284). Periaortic uptake may be associated with retroperitoneal fibrosis.

The IVC is normally located to the right of the aorta but there may be anatomic variants such as duplication. Bland thrombus may be present with or without FDG uptake (285,286), but tumor thrombus will be active and has been reported in association colon carcinoma (287), rectal carcinoma (288), renal cell cancer (289), adrenal cortical carcinoma (289), pancreatic cancer (289), and hepatocellular cancer (289). The most common tumors to invade the cava are renal cell carcinoma, HCC, and adrenal cortical carcinoma.

Retroperitoneal Fibrosis

Retroperitoneal fibrosis is a rare entity that leads to chronic inflammation and fibrosis in the retroperitoneum typically in the periaortic space but can involve the retroperitoneal

viscera, particularly the kidneys and ureters but could even involve the pancreas, duodenum, colon and bladder, small-bowel mesentery, and epidural space (290).

Two thirds of the cases are idiopathic but there are many secondary causes including certain medications, radiation, aortic aneurysms, trauma, malignancy, infection, and surgery (291). Men are affected more commonly than women and they tend to be middle aged. Both CT and MRI may be used for diagnosis. Imaging features in combination with laboratory data can help confirm diagnosis but their appearance can overlap with that of malignancy, particularly lymphoma and retroperitoneal sarcoma, and infection if it occurs in an atypical location such that biopsy may be warranted. CT imaging features include soft tissue mass encasing the aorta, IVC, and iliac vessels. Encasement of the ureters may cause obstruction and renal failure often leading to medial deviation of the mid and distal ureters, a sign typically described on IV pyelogram but can be seen with cross-sectional imaging particularly CT and MR urography. Enhancement of the soft tissue may indicate activity of disease and is helpful for determining extent of disease and complications such as obstruction. Activity on FDG PET fusing to the retroperitoneal mass will indicate continued activity of the disease and/or response to therapy (105,292,293).

Tumors

There are a wide variety of tumors that arise in the retroperitoneum. A tumor can sometimes be better characterized by the site, displacement, or distortion of normal organs and by any indication of vascularity on CT (294). Patterns of spread may also be helpful.

Leiomyoma

Retroperitoneal leiomyomas accumulate FDG (295). Lipomas are fat density and heterogeneous on CT (294). Ganglioneuromas are more common in children and young adults. Most extra-adrenal ganglioneuromas occur in the retroperitoneum (296). They tend to spread along the retroperitoneal spaces without compression of adjacent structures like blood vessels (294), spread along the sympathetic chain, and are often elongated in configuration. They may contain calcium, and may enhance mildly to moderately (294). On FDG PET, these lesions have been reported to demonstrate moderately increased activity (297).

Other neural tumors to consider are schwannomas, which can be variably FDG avid, but sometimes demonstrate intense activity (298–300), paragangliomas, which can accumulate FDG (301), and neurofibromas, which are usually not FDG avid unless they undergo malignant transformation (302). Schwannomas are well marginated

and relatively low attenuation on CT (294). Cystic changes and calcification are common features on CT (296). Parangliomas have a tendency to metastasize in up to 40% of cases (296). Neurofibromas may be associated with von Recklinghausen's syndrome, but more commonly occur in isolation. On CT, they are smooth, round, and show homogeneous enhancement (296).

Lymphangiomas are well-defined, cystic masses with little or no contrast enhancement. They can be locally invasive and require resection (303). While they are more common in young children, they do occur in adults (303).

Malignancy

Lymphomas, sarcomas, and malignant neurogenic tumors are the most common malignancies identified in the retroperitoneum. Lymphomas begin in the retroperitoneal lymph nodes and tend to spread along the retroperitoneal spaces and surround blood vessels (294). Their FDG avidity will depend on the histology of the lymphoma. They are rarely isolated to the retroperitoneum, and generally will have a distribution clearly related to discrete or confluent nodal masses.

Sarcoma

In general, retroperitoneal sarcomas have a worse prognosis than other sarcomas, probably because they tend to present later in their course with larger size (304). The sarcomas most commonly seen in the abdomen include liposarcoma, malignant fibrous histiocytoma, leiomyosarcoma, and in children, rhabdomyosarcoma (305).

Liposarcomas are the most common retroperitoneal sarcoma, and occur slightly more often in women. Histologically they are characterized as well-differentiated, pleomorphic, myxoid, and dedifferentiated. On CT, they will have variable amounts of fatty density with more fat in the lower grade tumors and less fat, almost indistinguishable, from other sarcomas. They are likely to be heterogeneous and irregular (294). On FDG PET, uptake tends to vary with the grade of malignancy in liposarcoma and will offer prognostic information (306).

Leiomyosarcomas will enhance moderately on CT (294) and can demonstrate necrosis. On PET, these will be hypermetabolic (307). While leiomyosarcoma tends to occur in the uterus, a rarer entity, inflammatory leiomyosarcoma, only occurs outside the uterus and has been reported in the retroperitoneum (308).

Malignant fibrous histiocytomas, when they occur in the retroperitoneum, tend to be large and, therefore, have a poorer prognosis. Complete surgical resection with wide margins offers the best outcome. When they recur after surgical resection, they generally present with metastases (309) for which FDG PET may be useful in identifying, since malignant fibrous histiocytoma is hypermetabolic in

FDG PET (307). It has been suggested that in the retroperitoneum, malignant fibrous histiocytomas represent dedifferentiation from liposarcomas (305).

Malignant nerve sheath tumors or neurofibrosarcomas can arise from malignant degeneration of neurofibromas, especially in the setting of NF-1 neurofibromatosis. FDG uptake will be an indication of malignant degeneration (302) and the degree of uptake appears to predict survival with very high accuracy (11). PET/CT has been useful in delineating the malignant portion of a degenerated neurofibroma and in identifying the extent of the primary tumor as well as the existence of metastases (310). On CT, they may be irregular and infiltrative (311). Their appearance on CT is unhelpful in distinguishing malignant nerve sheath tumors from neurofibromas (311).

Rhabdomyosarcoma

Rhabdomyosarcomas are the most common soft tissue tumor sarcoma in children, but are not very common in the retroperitoneum (312). However, when they originate in the retroperitoneum, they are usually fairly advanced. FDG PET alone has shown a high sensitivity and 77% specificity in evaluating the presence and extent of disease at presentation of the primary (313). Although CT is fairly accurate in identifying lymph node metastases in rhabdomyosarcoma (314), PET lacks specificity in evaluating lymph node involvement (315). In the evaluation of recurrence of rhabdomyosarcoma, PET/CT is more specific than MRI or CT alone and more sensitive for distant metastases than those conventional modalities (316).

Neuroblastoma

Only about one-third of abdominal neuroblastomas are extra-adrenal. They occur in children less than 10 years of age with predominance in males. On CT, they tend to be irregular, unencapsulated, and lobulated. Discrete or punctuate calcification is a common feature (296). Although MIBG scintigraphy is more commonly used, they may be positive on FDG PET and PET will be useful in identifying distant, e.g., bone marrow, metastases (317).

Abdominal Wall/Omentum and Peritoneum

Hernias

There are many types of abdominal hernias; of which, only a few will be discussed. Incisional hernias, parastomal hernias, umbilical, and inguinal hernias are commonly seen and may contain omental fat, small, or large bowel. The degree of herniation may be variable depending on patient positioning and provocative maneuvers. A portion of the bowel wall or entire loops of bowel may be present within the hernia sac. Obstruction should be excluded. The most common inguinal hernia is the indirect hernia, which passes through the inguinal ring and

typically extends into the scrotal sac in men or labia majora in women. Ascites fluid may also track into hernia sacs. Femoral hernias pass into the femoral canal along the common femoral vasculature. On FDG PET alone they have been sometimes mistaken for masses when their contents, e.g., bowel, is metabolically active; however, PET/CT usually obviates this problem.

Abdominal Wall Masses

Benign

Most commonly seen are hematomas usually related to the rectus abdominus muscle and may result from trauma or occur in patients on anticoagulation therapy. The hematoma may be higher in attenuation than adjacent muscles because of acute hemorrhage or may show a fluid-fluid or “hematocrit” level with fluid density serum and dependent blood products. Active hemorrhage may be apparent on postcontrast imaging with active extravasation of hyperattenuating contrast. Rim enhancement may be present, and as the hematoma evolves it usually becomes lower in density, ultimately developing into a seroma which should resolve over time.

Infection may complicate hematoma or develop because of penetrating trauma or postsurgical intervention. Enlargement of the abdominal wall musculature, rim enhancement, either smooth or irregular, and adjacent fat stranding may be present. Gas may also be present and may indicate the presence of an enterocutaneous fistula.

Endometriotic implants may have soft tissue density or be hemorrhagic masses with enhancement. Endometriosis may be FDG avid (77). Implants will typically occur in a postsurgical site in the subcutaneous tissue or abdominal muscles as a result of prior uterine surgery such as Caesarean-section. Underlying endometriosis is not necessarily present.

Desmoid tumors, which are locally aggressive benign tumors, have a similar appearance to endometriosis but evidence of hemorrhage is absent. MRI is more sensitive for detection of blood products.

Metastases can occur within surgical wounds via direct extension or implantation via hematogenous spread. They may be located in the subcutaneous tissue or abdominal wall muscles. Periumbilical metastases, (referred to as Sister Mary Joseph nodes) may be seen. Metastases from GI or ovarian primaries behave this way more commonly. On PET/CT, these soft tissue masses at the abdominal wall will be FDG avid (Fig. 16 of chap. 11). Varices from portal hypertension related to cirrhosis should also be considered.

Ascites

Fluid within the peritoneal cavity may result from increased fluid production or inadequate resorption of

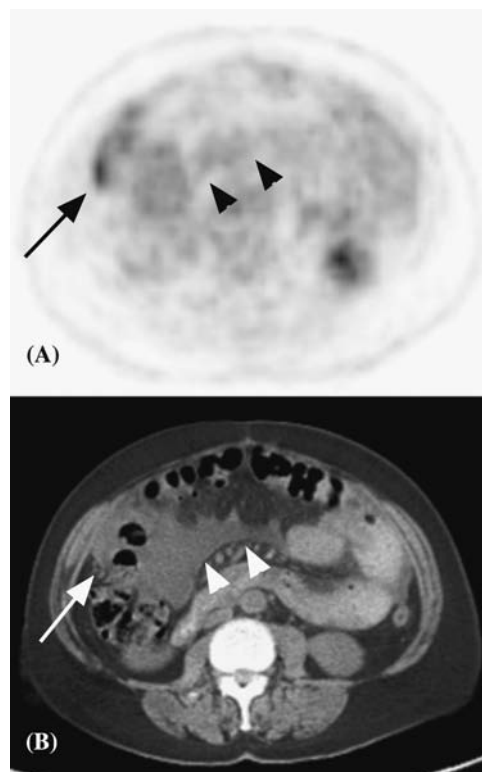


Figure 48 (A) PET slice shows mild activity (*arrowheads*) in the mesentery and surrounding the transverse colon corresponding to ascites on unenhanced CT (B). More intense uptake fuses to a discrete peritoneal implant in this patient with metastatic gastric carcinoma (*arrow*). *Abbreviations:* PET, positron emission tomography; CT, computed tomography.

fluid. Common benign causes include congestive heart failure, cirrhosis, hypoalbuminemia, lymphatic obstruction, infection, inflammation, bowel obstruction, stomach or small-bowel perforation, and ischemia. Fluid may be focal or loculated or freely disseminating. Focal collections may indicate infection, inflammatory, or neoplastic processes (Fig. 48). Density may vary ranging from simple fluid to hemorrhage. Ascites in the setting of noninflammatory and benign disease will be hypoactive (318). Cystic metastatic implants may mimic ascites but tend to displace structures and exhibit mass effects. Nodularity or soft tissue in the omentum or soft tissue implants is concerning for malignancy and, in general, will be metabolically active on PET (Fig. 41).

Abscesses

Intra-abdominal abscesses are fluid collections with rim enhancement that may contain gas. These collections are extraluminal. Positive oral contrast is useful for differentiating fluid and gas within the bowel from extraluminal collections. 3D reconstructions are also helpful for tracing the bowel loops and determining whether collections are

extrinsic to bowel loops. Foreign bodies from prior surgery can lead to abscess formation as well as perforation of a viscus.

Carcinomatosis

Peritoneal carcinomatosis is the most common neoplasm in the peritoneum and can occur with a variety of tumors, most frequently metastatic ovarian, colon, or stomach cancer. Omental thickening, soft tissue nodularity, and masses may be seen. Implants along the serosal surface of the liver and spleen may be present as well as implant along the bowel surface, which can lead to obstruction. Sensitivity of FDG PET alone varies (55,319,320) with reports of 30% to 66%. The combination of PET and CT has shown improved sensitivity and positive predictive value for identifying peritoneal disease (319), with abdominal wall disease most easily discerned on FDG PET (320). While the increment in identification of disease may be small to moderate with the addition of PET, FDG PET often adds information that changes management (55,203,320,321). While PET/CT may only augment CT alone in the diagnosis of untreated disease to a modest degree, it will be particularly helpful in evaluating the response to therapy since soft tissue may lag in resolution but not in metabolic activity (203). Nonetheless, neither PET/CT nor CT alone has been found adequate to quantitate the amount of peritoneal disease (322). Endometriosis may cause serosal implant and can mimic malignancy. On FDG PET tuberculous peritonitis has been reported to mimic carcinomatosis (323,324). Lymphoma can also become disseminated in the peritoneal cavity.

Lymphadenopathy

Mesenteric adenitis

Mesenteric adenitis may present clinically as right lower quadrant pain. It may be primarily due to an infectious etiology or secondary to an intra-abdominal inflammatory process such as appendicitis, right-sided diverticulitis, or Crohn's disease (325). Features of primary adenitis include right lower quadrant, mesenteric, and occasionally retroperitoneal lymphadenopathy, with mild thickening of the terminal ileum, and are relatively uncommon in adults.

Peritonitis

Peritonitis or inflammation in the peritoneal cavity is usually due to infections or a ruptured viscus and is manifested by ascites and peritoneal wall enhancement, although nodularity and low attenuation lymphadenopathy are seen in the setting of tuberculous peritonitis. Tuberculous peritonitis will be intensely active and imitate peritoneal carcinomatosis on FDG PET (323,324). In

patients undergoing peritoneal dialysis who develop acute sclerosing peritonitis, FDG PET has been positive. It becomes less positive in the more chronic phase, but may be useful in assessing patients in whom peritoneal dialysis loses efficacy (326).

SUMMARY

PET/CT has a well-established role in the staging and monitoring of esophageal cancer and colorectal cancer. PET/CT is useful in the diagnosis (incidental), staging, restaging, and in evaluating for recurrence, metastases, and treatment response of these tumors. Its application in gastric carcinoma and primary tumors of the pancreas, biliary tract, and liver is less well established because of somewhat variable avidity of FDG for these tumors. Nonetheless, many cases in the literature of important changes in management because of upstaging, and occasionally, down staging have been discussed. Neuroendocrine tumors of the pancreas tend to fall in this category as well.

PET/CT has added enormously to the evaluation of the adrenals in patients with known primaries or even unexpected masses or uptakes. Retroperitoneal processes, both non-neoplastic and neoplastic will accumulate FDG. Using the configuration on CT is helpful to differentiate, and PET will be important in monitoring activity. For many of the nonlymphomatous neoplasms that occur in the retroperitoneum, MRI will be the imaging modality of choice, however. Finally, in the peritoneum, FDG PET alone lacks sensitivity but adds to the specificity of CT and will, in many cases, identify disease otherwise missed on CT alone.

Although false positives and false negatives may challenge the application of PET/CT, appropriate integration of the anatomic information, clinical information, and metabolic findings may assist in limiting these confounding factors. Finally, incidental PET uptakes and CT findings may occur, which require description or at least sufficient understanding so that further evaluation can be undertaken as warranted.

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PET/CT in Gynecologic Malignancies

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INTRODUCTION

Positron emission tomography/computed tomography (PET/CT) has no formal role in the detection of gynecologic malignancy except in very isolated instances when a patient presents with an unexplained paraneoplastic syndrome, as sometimes occurs with ovarian carcinoma. Otherwise, the role of fluorodeoxyglucose (FDG) PET/CT in gynecologic malignancies should be confined to staging, monitoring recurrence, and monitoring treatment. These applications have been established clearly for cervical carcinoma. In addition, the formulation of radiation treatment plans using metabolic data, and now metabolic data fused to a CT scan, is receiving increasing attention. A growing body of work also supports all of these applications in ovarian carcinoma. While the basis for staging of endometrial carcinoma with FDG PET/CT is weaker, the case for its use in monitoring recurrence and following response to therapy in metastatic disease is increasingly strong. Furthermore, normal adnexa and endometrium may accumulate FDG, making it essential to understand both the normal circumstances under which this occurs, as well as the CT findings which should prompt further investigation of an incidental adnexal or uterine uptake or mass.

TECHNICAL ISSUES

Knowledge of the patient's menstrual status and the timing of the cycle can explain the unexpected uptake of radio-tracer in adnexa or endometrium and should be obtained through a patient questionnaire or interview. To optimize the quality of the information obtained with PET/CT, attention to patient history and technique is critical.

PET Acquisition

Most literature describe studies done in a fairly standard way, using a four to six hours' fast, ensuring that blood glucose is between 80 and 150 mg/dL and with a 45 to 60 minutes' incubation period. However, in the evaluation of the pelvis, a number of authors have suggested that accuracy can be improved by eliminating bowel and urinary activity. Thus, rarely, the use of a bowel prep with magnesium citrate the night before, in combination with a more prolonged fast, has been used successfully to clear colonic activity (1). Bowel activity is more easily identified and is less of a problem with PET/CT, although occasionally focal uptake may still be difficult to assign anatomically to either pelvic lymph nodes or bowel. Of course, to take full

advantage of the anatomic information provided by CT, oral and intravenous (IV) contrast should be used.

Some investigators have advocated the use of hydration, diuretics, and bladder catheterization and/or saline lavage to eliminate bladder and ureteral activity. While many imagers do without these aids, an improved sensitivity and specificity has been obtained with this technique. Hydration is begun 30 minutes after FDG is administered using IV 0.45% saline at a rate of 1000 mL/hr. A Foley catheter is placed at this time. In the protocols described, imaging begins at the base of the skull, and furosemide (0.3 mg/kg) is administered about 20 minutes prior to imaging of the abdomen and pelvis. For faster PET crystals, this procedure might mean administering the diuretic during the uptake period. Just before imaging the field of view encompassing the bladder, the Foley catheter is clamped, and the bladder may be filled retrograde with sterile normal saline (1). Others have used continuous manual bladder irrigation to improve visualization of the pelvis (2).

With PET/CT, ureteral activity is somewhat less problematic, especially in patients with some intra-abdominal fat, but intense bladder activity can still overshadow subtle foci and cause artifacts. Alternatively, prone imaging of the pelvis or post-void imaging of the pelvis may help (3).

Modifications for RT Planning

The addition of diuretics and bladder catheterization becomes even more critical if PET/CT is to be used for radiation treatment planning, as it sometimes is in cervical carcinoma (4). For treatment planning, the position of the bladder may need to be reproduced, and the angle and position of the cervix and the uterus may require a reproducible position, achieved by using brachytherapy applicators (5). In fact, these authors have included an additional study using FDG-filled applicators to situate the applicator in relation to the tumor (4). With PET/CT, the additional acquisition might be unnecessary. Nonetheless, filling the bladder with (nonradioactive) saline will help to identify the primary tumor (1). A post-void image of the pelvis may afford the same benefit (3). This image becomes important in those algorithms where FDG PET is used to help determine tumor volume (6).

CT Acquisition

Scanning protocols for PET/CT evaluation of the pelvis have not yet been standardized. Multidetector CT (MDCT) has largely replaced the single-slice CT, allowing for better evaluation of the uterus, adnexa, and other pelvic structures. With the acquisition of larger volumes, MDCT provides thinly collimated images with less

volume averaging and much greater resolution. Off-axial reformatted images in the coronal and sagittal planes can be generated from these data sets and can prove particularly useful in the assessment of gynecologic malignancies. In conventional CT imaging of the female pelvis, administration of oral and IV contrast is imperative. Bowel opacification with positive oral contrast, such as dilute barium, typically used in PET/CT, allows differentiation of fluid-filled bowel from pelvic masses, particularly cystic masses. Imaging should be performed at least one hour after oral contrast administration to allow for adequate luminal opacification. Some authors advocate using water for bowel opacification, as this allows for improved detection of calcified tumor implants (7). Bolus administration of IV iodinated contrast material is required for definition of pelvic anatomy and for differentiating iliac blood vessels from lymph nodes (8). The use of orally administered low-density barium has been shown to improve bowel definition at PET/CT imaging without causing significant artifacts (9).

However, the use of both oral and IV contrast in combined PET/CT systems has not been widely established. Potential drawbacks include the requirement for whole-body coverage and possible adverse effects on the CT-based attenuation correction for PET. In practice, artifacts are minimal and can usually be identified by comparing of the attenuation-corrected PET images with the uncorrected images. Antoch et al. (10) used a protocol of 750 mL of glucose-free barium for oral contrast at a concentration of 1.5 g barium sulfate/100 mL. Immediately before imaging, the patient drank another 250 mL of barium. They also administered IV iodinated contrast (300 mg/mL) with an automated injector. Contrast material of 80 mL was administered at a flow rate of 3 mL/sec for arterial enhancement of the head and neck. CT was started at a delay of 30 seconds. This was followed by another 60 mL, administered at a flow rate of 2 mL/sec. These authors found that the administration of oral and IV contrast materials-enhanced CT image quality by permitting delineation of vascular and intestinal structures without compromising PET image quality. This dual phase protocol of contrast resulted in good intravascular enhancement in all body regions.

NORMAL FINDINGS

Ovaries

CT Findings

To recognize the ovaries at CT (Fig. 1), one should be familiar with their morphologic features as well as relationship to adjacent structures such as the ureter, ovarian vein and artery, and ligamentous attachments. The ovaries are paired, ovoid, or almond-shaped structures with

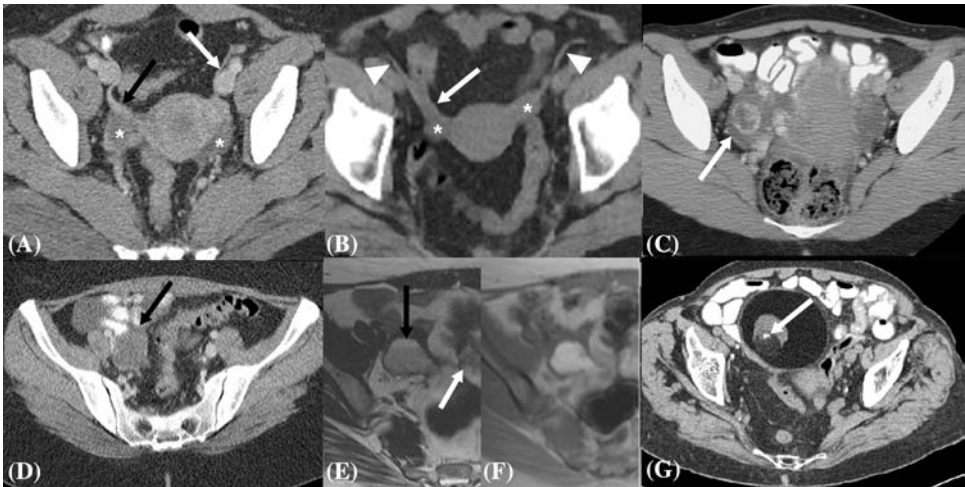


Figure 1 Normal ovaries and benign variants. (A) Normal ovaries. Axial image from contrast-enhanced CT scan obtained in a 30-year-old woman demonstrates normal ovaries located on either side of the uterus (*asterisks*). The uterine-ovarian ligament is a linear soft tissue structure extending between the body of the uterus and the ovary (*black arrow*). The left external iliac artery and the vein (*white arrow*). (B) Noncontrast CT scan in a different patient demonstrates the normal ovaries (*asterisks*). The broad ligament appears as a broad-based soft-tissue band arising from the lateral aspect of the uterus (*arrow*). The round ligament emerges from the broad ligament and enters the internal inguinal ring (*arrowhead*). (C) Axial contrast-enhanced CT scan in a 35-year-old woman. A cystic lesion in the right ovary has a thick, crenulated enhancing wall (*arrow*). This is the typical CT appearance of a corpus luteal cyst often visualized in the periovulatory phase of the menstrual cycle. This should not be misinterpreted as a pathologic finding. (D) Right adnexal cystic mass with cyst contents measuring higher than simple fluid attenuation (*arrow*). At CT, this appearance is nonspecific, but could be compatible with an endometrioma. (E) T2-weighted axial MR image demonstrates that this mass contains a fluid/fluid level (*black arrow*). The lower-signal intensity dependent component represents T2 loss of signal due to the presence of hemosiderin from chronic bleeding into the lesion. This finding is more specific for an endometrioma. Linear areas of decreased signal intensity in the pelvic fat represent fibrosis/adhesions (*white arrow*). (F) T1-weighted axial MR image in the same patient shows the cyst contents are high-signal intensity, compatible with blood. Endometriomas are usually high-signal intensity on T1. (G) Contrast-enhanced CT image demonstrating a large right adnexal mass which is mostly fat attenuation, containing a central soft tissue nodule with calcification (*arrow*). This is the typical CT appearance of a dermoid, or mature cystic teratoma.

variable morphology depending on patient age, hormonal status, and stage of menstrual cycle (11). The adult ovary is approximately 2.5 to 5 cm long, 1.5 to 3 cm wide, and 1 to 2 cm thick. Ovarian volume is the preferable way to assess ovarian size for normalcy. This volume is calculated with the formula for a prolate ellipse ($0.523 \times \text{length} \times \text{width} \times \text{thickness}$). There are no values found in the literature for normal ovarian volumes as delineated at CT imaging. However, values for mean ovarian volume as determined at sonography do exist (12) (Table 1). Normal ovaries in patients of childbearing age usually contain

follicles or physiologic cysts, which appear as fluid attenuation areas at CT. If there are many very small follicles, the ovary may appear as uniform low attenuation. If there are no follicles, the ovaries demonstrate uniform soft tissue attenuation and may be more difficult to recognize. Postmenopausal ovaries are small and often not identified since they do not contain follicles or physiologic cysts (13). Follicular activity is usually not present four to five years after menopause.

The ovaries are usually located within the ovarian fossa, the boundaries of which include the ureter and internal iliac vessels posteriorly, the broad ligament, mesovarium, and hilus of the ovary anteriorly, the external iliac vessels superiorly, and the ovarian ligament medially (14). The ovary is usually located anterior or anteromedial to the ureter at either side of the uterus. The suspensory ligament (infundibulopelvic ligament) is derived from the superolateral part of the broad ligament, attaches the ovary to the pelvic sidewall, and contains the ovarian vein and artery (Fig. 1) (14). At CT, this ligament may appear as a short and narrow, fan-shaped soft tissue band that widens as it approaches the ovary and is slightly

Table 1 Mean Volumes of Normal Ovaries Established for Ultrasonography

Hormonal status	Mean volume (cc)	95% confidence interval (cc)
Premenarche	3.0	0.2–9.1
Menstruating	9.8	2.5–21.9
Postmenopausal	5.8	1.2–4.1

Source: From Ref. 12

thickened at the ovarian attachment (Fig. 1) (11). The ligament is best recognized by tracking the ovarian blood vessels caudally to the adnexa. When visualized on axial CT, it usually extends from the ovary along the direction of the external or common iliac vessels. The utero-ovarian ligament extends from the uterine end of the ovary to the uterine cornu and is enclosed in the two layers of the broad ligament (14). This ligament may be visualized at CT as a short and narrow soft tissue band located between the uterus and the ovary. The variable position of the ovaries is, in large part, related to the laxity of these ligaments. Ovarian position is also influenced by uterine size, ovarian size, degree of urinary bladder distention, and degree of distention of the rectosigmoid colon. The broad ligament is a double fold of peritoneum that extends from the lateral uterine margins to the pelvic sidewalls and incompletely divides the true pelvis into anterior and posterior components. The majority of the fallopian tube is contained within the broad ligament. The mesovarium is a short, double-layered peritoneal fold that extends from the posterior layer of the broad ligament and attaches to the anterior border of the ovary. The ovarian blood vessels and lymphatics are contained within the mesovarium. The broad ligament and the mesovarium are usually not visible on CT, unless surrounded by ascites. The ovaries may be

visualized suspended from the posterior surface of the broad ligament in this setting.

Young patients who are to undergo therapeutic irradiation of the pelvis may have the ovaries surgically transposed out of the radiation field. The ovaries and suspensory ligament with the ovarian blood vessels are mobilized and usually repositioned laterally to the lower paracolic gutters near the iliac fossa or to the posterior intraperitoneal space in the upper pelvis, lateral or anterolateral to the psoas muscle (15,16). Knowledge of this surgical history will aid in the identification of the transposed ovary and avoid misinterpretation as an abnormal finding.

Differentiating the ovaries from enlarged lymph nodes may present a diagnostic challenge. The ovaries are intraperitoneal and located internal to the parietal peritoneum. The lymph nodes at the pelvic sidewall are extraperitoneal, located lateral or posterolateral to the ureter and in close proximity to the iliac vessels and sidewall musculature (11). A large lymph node at the pelvic sidewall may displace the ureter medially or anteromedially and may efface or encase the iliac vessels or efface the sidewall musculature (17). An ovarian mass may displace the ureter posteriorly or posterolaterally.

The differential diagnosis of ovarian masses (Figs. 1, 2) varies with age and hormonal status of the patient. In

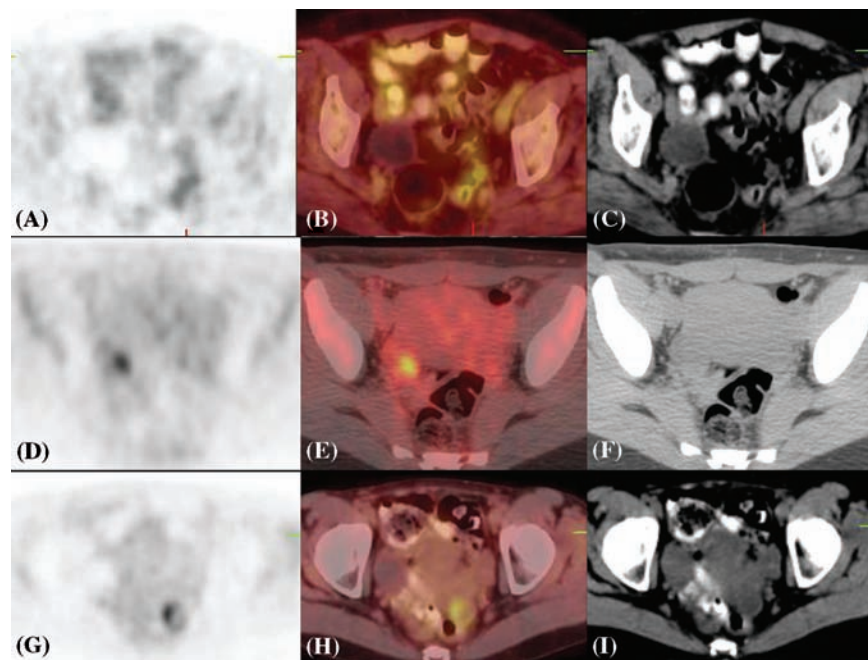


Figure 2 PET/CT of the normal ovary. Transaxial FDG PET (A), fused PET/CT (B), and CT (C) alone performed in a 32-year-old woman with newly diagnosed breast cancer show absence of uptake in the well circumscribed, uniformly low attenuation, benign, right adnexal cyst. FDG PET (D), fused (E), and CT (F) slices through the pelvis of a 37-year-old woman with breast cancer show focal uptake in a more solid-appearing, small right ovary. Her last menstrual period was 16 days prior to the PET/CT. PET (G), fused (H), and CT (I) images performed day 21 of the menstrual cycle in another young woman with newly diagnosed Hodgkins disease shows uptake fusing to the rim of the left adnexa with a luteal cyst. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography.

reproductive-aged women, the most common type of ovarian mass is a benign functional cyst related to the menstrual cycle. These include follicular, theca lutein, and corpus luteum cysts. CT features of a benign adnexal cyst include a cyst that is well circumscribed, less than 5 cm in size, and of uniform low attenuation (13,18). However, thin septations, increased attenuation, or focal wall thickening have been reported in up to 33% of benign cysts (19). Corpus luteal cysts are normal physiologic ovarian structures, which form after ovulation by the dominant follicle. The follicular wall becomes vascularized, thickened, and partially collapsed. The changes in the follicular wall are known as luteinization and are associated with the secretion of estrogens and progesterones by the ovary in the second half of the menstrual cycle. At CT, the corpus luteal cyst is readily recognizable as it is typically unilocular, less than 3 cm in size with a thick, crenulated, or hyperdense wall (20).

The likelihood of malignancy increases with increasing complexity of an ovarian cyst (19). CT features of an ovarian mass suggestive of malignancy include thick walls and septae greater than 3 mm in thickness, papillary projections, multiple loculations and solid components, lobulated solid mass, and large sized (>4 cm) (8,21). However, endometriomas (Fig. 1), tubo-ovarian abscess, and some benign cysts, such as hemorrhagic cyst, demonstrate a complex appearance with considerable overlap in imaging features. Metastatic disease to the ovaries has a nonspecific appearance and may be primarily cystic, solid or mixed solid, and cystic (Figs. 3 and 4).

In a retrospective review of CT scans in 3448 women, Slanetz et al. (22) found an incidental adnexal lesion in 168 (5%) of them. In the 151 patients among whom follow-up was available, 69 were premenopausal and 82 postmenopausal. Lesions on CT were predominantly cystic in 99, predominantly solid in 45, and ill defined in 7.

Overall, 69% were found to have a benign lesion, 30% had undetermined lesions, and 1% (2 patients) had metastatic ovarian implants. These two patients had a known primary malignancy. The adnexal lesions in the patients with metastases were heterogeneous, predominantly solid and larger than 4 cm in size. No primary ovarian malignancies were incidentally discovered. These authors conclude that in most cases an adnexal lesion that is incidentally discovered at CT imaging is benign. Postmenopausal patients should have one follow-up imaging study to characterize the lesion definitively, to document resolution, or at least ensure stability, especially if larger than 3 cm and with a heterogeneous, predominantly solid appearance. In all age groups, more complete characterization of the internal components of a complex adnexal mass detected at CT may require ultrasound (US) assessment to exclude ovarian neoplasm (19,21).

FDG PET Findings

The metabolic appearance of normal adnexa ranges from hypometabolic to rim-like uptake to intense focal spheroid uptake (Fig. 2). Encountering increased focal uptake in the adnexa of a premenopausal woman can be unsettling. More often than not, the uptake represents a corpus luteum or an ovarian follicle (23) occurring around ovulation in the late follicular, ovulatory, and early- and mid-luteal phases, with the early luteal phase being most frequent (23,24). Normal adnexa are more likely to appear with spheroid focal uptake prior to day 17 of the menstrual cycle. While adnexal uptake may be seen in premenopausal women with either oligomenorrhea or regular menstrual cycles, it should not be seen in amenorrheic, premenopausal women or postmenopausal women (23,24). Often a menstrual cycle history can be useful in differentiating benign from malignant adnexal uptake. Although the standardized uptake values

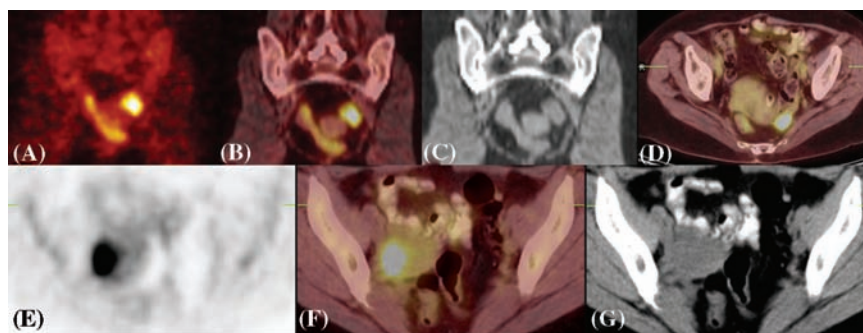


Figure 3 Primary ovarian tumors. Coronal PET (A), fused (B), CT (C), and transaxial fused PET/CT (D) performed in an 84-year-old woman with a history of breast cancer. The left adnexal mass had increased in size but was stable in intensity (SUV 7) over a three-month period. Activity in the adnexa of a woman this age should raise suspicion for malignancy. FDG PET (E) performed in a 56-year-old woman with recurrent gastric carcinoma now metastatic to the right ovary, a so-called Krukenberg tumor. Activity fuses (F) to only a portion of the mass seen on CT (G). *Abbreviations:* PET, positron emission tomography; SUV, standardized uptake value; FDG, flourodeoxyglucose.

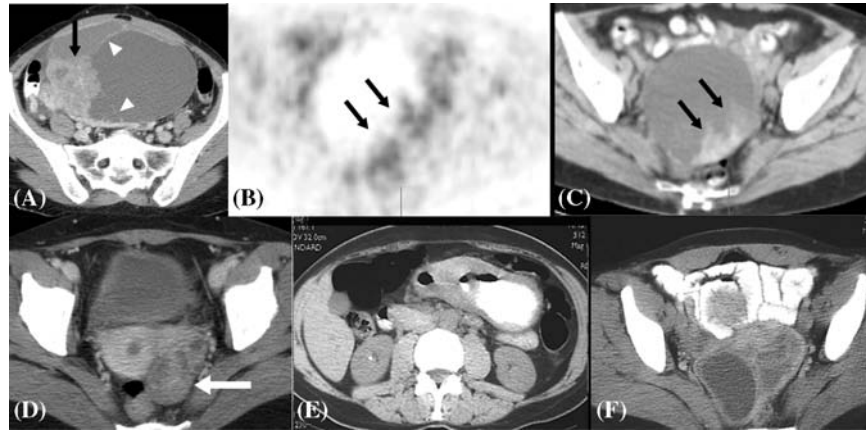


Figure 4 Primary ovarian tumors (*continued*). (A) Large complex solid and cystic mass containing septations (*arrowheads*) and large soft tissue component (*arrow*) occupying the lower abdomen and pelvis. Pathology showed an endometrioid adenocarcinoma of the ovary. Transaxial FDG PET (B) through a pT1a mucinous cystadenoma of the ovary shows a photopenic region corresponding to the cystic portion of the tumor seen on CT (C) and only very mild uptake corresponding to the solid, and partially calcified, mucinous adenocarcinoma (*arrows*). (D) Granulosa cell tumor of the left ovary (*arrow*). CT demonstrates completely solid left ovarian mass with heterogeneous contrast enhancement. (E) CT of the upper abdomen demonstrates mural thickening of the gastric antrum representing primary gastric adenocarcinoma. (F) Bilateral primarily cystic ovarian masses consistent with metastatic disease (Krukenberg tumors). *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography.

(SUVs) are variable, Lerman et al. separated benign from malignant ovarian uptake with an SUV of 7.9 yielding a sensitivity of 57%, specificity of 95%, positive predictive value (PPV) of 85%, and a negative predictive value (NPV) of 80% on the basis of the receiver operating curve analysis (24). These authors have also described uptake in serous and mucinous cyst adenomas, dermoid cysts, endometriosis, teratomas, and tubo-ovarian abscesses. (25,26).

Uterus

Normal CT Appearance

At CT, the uterus demonstrates a highly variable appearance related to the positioning of the uterus in the pelvis, patient age, hormonal status, and parity (13). If the uterus is anteverted or anteflexed, it is located superior and posterior to the urinary bladder (Fig. 5). If the uterus is retroverted (Fig. 5 D), the fundus is located in the cul-de-sac. The fundus may also be deviated laterally to either side of the pelvis. The uterus is a pear-shaped organ measuring approximately 8 cm × 5 cm × 2.5 cm or 9 cm × 6 cm × 4 cm in length, width, and thickness for nulliparous and multiparous women, respectively (14). The uterine body appears more triangular in shape, whereas the cervix is more rounded (27). The walls of the uterus are smooth in contour and demonstrate uniform attenuation. After IV contrast, the myometrium enhances more than the other pelvic soft tissues because of its rich blood supply (28,29). Vascular calcifications within intra-uterine arterial vessels may be present in the outer myometrium, most frequently seen in the older patient.

These appear as linear, branching calcifications located at the periphery of the uterus. The endometrial cavity is centrally located and enhances to a lesser extent than the myometrium. In women of reproductive age, the endometrial canal is typically 5 to 15 mm in thickness (13). Fluid of variable quantity may be present within the endometrial cavity depending on the phase of the menstrual cycle. In postmenopausal patients, the endometrial tissue is atrophic and, therefore, the endometrium is less prominent. At CT, the reported upper limits of normal for short-axis endometrial thickness in an asymptomatic postmenopausal woman is approximately 12 mm, which is higher than the 8-mm value used at sonography (30). This discordance is likely related to differences in imaging planes for CT versus US. Thickening of the endometrium or fluid in the endometrial canal in the postmenopausal patient should prompt further evaluation by US to exclude endometrial mass or other abnormality.

The cervix is the lower one-third of the uterus, usually measuring approximately 2 to 3 cm in length (7). On true axial images, it may be difficult to differentiate the exact demarcation between the uterus and cervix. The outer margins of the normal cervix are smooth and regular. At dynamic contrast-enhanced CT, the central inner zone of the cervix may show marked enhancement corresponding to the highly vascular cervical epithelium, whereas the more peripheral fibrous stroma demonstrates only intermediate enhancement (17). Inclusion cysts (Nabothian cysts) may be visualized if they have fluid attenuation. The lower aspect of the cervix is surrounded by the vaginal fornix, which is generally H-shaped in the axial

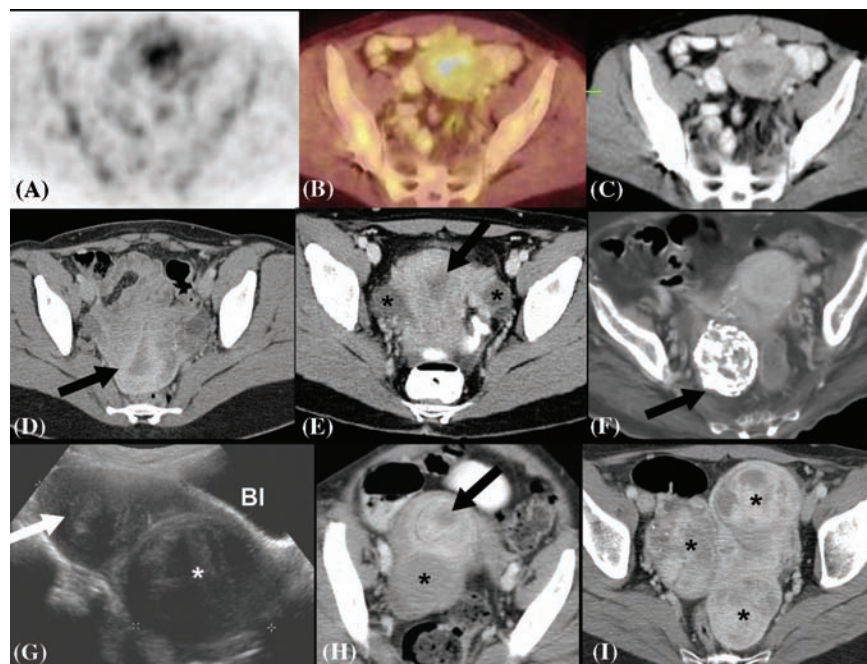


Figure 5 Uterus: normal variants and benign entities. FDG PET (A), fused (B), and CT (C) from a 45-year-old woman whose last menstrual period was 27 days ago. The PET shows mild uptake fusing to the lower attenuation endometrial cavity seen on CT. (D) Contrast-enhanced CT from another patient with a retroverted uterus seen well in the transaxial plane. The triangular-shaped endometrium (*arrow*) enhances to a lesser degree than the myometrium. (E) Contrast-enhanced CT from a different patient demonstrating an anteverted uterus. The endometrium is again visualized (*arrow*). The normal ovaries are demonstrated on either side of the uterus (*asterisks*). Contrast-enhanced CT (F) demonstrating a coarsely calcified uterine fibroid (*arrow*). (G) Sagittal transabdominal US of the pelvis demonstrates a large posterior lower uterine body subserosal fibroid (*asterisk*), uterine fundus (*arrow*). (H) Axial contrast-enhanced CT image in the same patient showing the subserosal fibroid which demonstrates decreased contrast enhancement secondary to degeneration (*asterisk*). An additional more uniformly enhancing submucosal fibroid is also present (*arrow*). Contrast-enhanced CT (I) shows multiple subserosal fibroids (*asterisks*), exophytic from the uterine surface. Heterogeneous contrast enhancement is secondary to areas of degeneration within these fibroids. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography; BI, bladder.

plane. A tampon placed in the vagina may help to better delineate the cervix at CT.

Endometrium on FDG PET

Endometrial cavity uptake is a common finding and, very often, a normal one (Fig. 5). It may be seen in both postmenopausal and premenopausal women. Relatively more intense uptake may be encountered during menstruation and somewhat lesser uptake during ovulation (24). The intense uptake that may be encountered during menstruation may also be seen in women who are oligomenorrheic, but in patients who are amenorrheic, uptake is less and similar to the postmenopausal endometrium. Uptake is statistically significantly lower during the secretory and proliferative phases. Oral contraceptives do not affect uptake.

FDG uptake is encountered fusing to a normal-appearing uterine cavity/endometrium in many postmenopausal women and should not be a cause for concern if the SUV

hovers between 1 and 3. The sensitivity and specificity of this uptake has not been studied. The effect of hormonal therapy or estrogen antagonists like tamoxifen and raloxifene in postmenopausal women has not been studied extensively, but in a limited series did not cause a marked increase in endometrial uptake (24). On the other hand recent curettage, endometriomas, and fibroids may cause increased FDG uptake (24,31,32).

SUVs as high as 16.6 have been reported in the endometrium during normal menstruation, but this value does not necessarily represent the upper limits of normal menstruation. In the series by Lerman et al., SUVs averaged 5 ± 3.2 (standard deviation). There was significant overlap with values encountered in women with cervical or endometrial cancers in one series (24), but in another, while there was overlap, SUVs associated with endometrial malignancies were significantly higher, averaging 6.0 ± 3.3 compared with 1.7 ± 1.1 for nonmalignant endometria in a series of 41 women with suspected malignancy of either the ovary or the uterus (2). Using 2.0

as a cutoff, the receiver operating curve analysis yielded a sensitivity of 100%, a specificity of 86%, a PPV of 97%, and an NPV of 100%. The accuracy was 98% for differentiating benign from malignant.

FIBROIDS

PET Findings

FDG uptake in uterine fibroids may be isointense with normal uterus, more intense, and sometimes heterogeneous (Fig. 6). Uptake has been associated not only with degenerating fibroids but with pathologically bland uterine fibroids as well (31,32).

Some authors have also identified increased SUVs in uterine sarcomas, but have described only a very small series of patients (33). In those patients the tumors were all identified on FDG PET alone, but the SUVs ranged from 3.0 to 6.3. Interestingly, FDG detected more cases than magnetic resonance imaging (MRI), which is considered the gold standard of imaging in this entity. The PET/CT combination for identifying malignant degeneration of fibroids may be even more useful, but the accuracy of differentiating benign from malignant uptake has not been adequately studied.

CT Findings

Comparison with CT may help to clarify the FDG PET uptake. Fibroids, or leiomyomata, are the most common

disorder of the uterus (Fig. 5). US is usually diagnostic and serves as the first-line imaging modality of choice in the patient with an enlarged uterus on physical exam and suspected fibroids. CT is not recommended or usually performed for primary evaluation. However, given the high prevalence of fibroids in women, fibroids are often encountered as an incidental finding at CT imaging. CT may also serve as a helpful adjunct when US findings are equivocal or for preoperative evaluation. The CT appearance of fibroids is variable depending on size, location (subserosal, intramural, or submucosal), composition and degree of degeneration, hemorrhage, or infarction. Typical CT features include enlargement of the uterus with a lobulated surface contour, focal myometrial thickening, or a focal uterine mass with or without calcification (34–36). Often, there is associated distortion of the endometrial cavity, particularly in the setting of a large fibroid or submucosal fibroid. Calcifications may also be noted, with variable appearance, including mottled, whirled, speckled, popcorn, or rim. The presence of coarse, dystrophic calcification in a uterine mass is the most specific sign of a uterine fibroid; however, this is a relatively uncommon finding, found in approximately 10% of fibroids (27). Fibroids demonstrate variable attenuation and may be hypodense, isodense, or hyperdense to the normal myometrium. There will also be variable contrast enhancement depending on the degree of vascularity. Low-attenuation areas may be present in a leiomyoma because of hyaline or cystic degeneration, necrosis, or

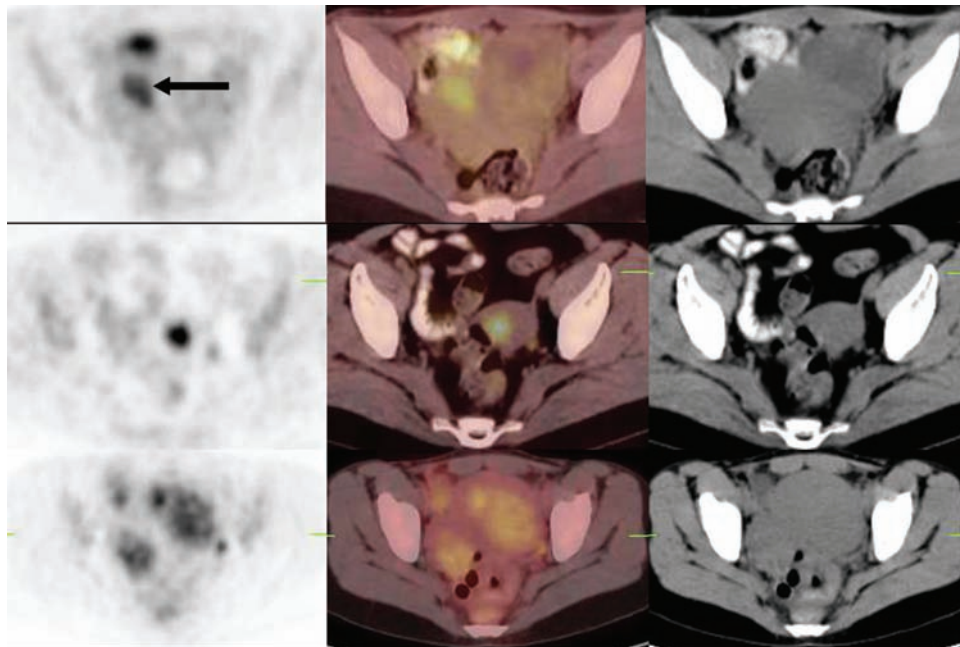


Figure 6 Uterine fibroids (*top row*). In a patient evaluated for a solitary pulmonary nodule, FDG PET shows moderately intense uptake (*arrow*) that fuses to a portion of a large fibroid seen on CT. (*Middle row*): Eccentric focal uptake was seen on FDG PET fusing to the myometrium suggestive of an intramural fibroid in a 39-year-old woman with breast cancer. (*Bottom row*): FDG PET performed in a 45-year-old woman with breast cancer showed mild heterogeneous uptake that fuses to a uterine fibroid on CT. *Abbreviations*: FDG, fluorodeoxyglucose; PET, positron emission tomography.

infarction. Lipomatous tumors of the uterus are rare benign tumors containing variable amounts of mature lipocytes, smooth muscle, and fibrous tissue. Lipoleiomyomas may result from fatty degeneration of a preexisting fibroid. Clinically, these growths are present in a similar fashion as fibroids, and they are readily recognized at CT because of the presence of fat within the lesion (37).

A pedunculated subserosal fibroid may be located in the adnexa, iliac fossa, anterior to the aortic bifurcation, or in the upper abdomen and may be difficult to differentiate from a primary solid ovarian mass. Multiplanar reformatting images may be helpful in confirming uterine origin. If this situation is encountered, US may also help to confirm uterine origin of the mass or identify normal ovaries, thereby excluding an ovarian mass. However, associated sound attenuation may impede or limit US evaluation, particularly if the fibroid is very large. MRI serves as a very helpful problem-solving tool in this setting. Rarely, a pedunculated fibroid may become completely detached from the uterus, develop its own blood supply, and appear as a solid mass in the pelvis, particularly the broad ligament. Sarcomatous degeneration is an infrequent complication of fibroids, occurring in less than 1% (27) of patients. On CT scans, it is impossible to distinguish a leiomyosarcoma from a preexisting benign fibroid unless sudden accelerated growth of a previously stable lesion or metastatic disease is identified. Especially in a postmenopausal woman, sudden growth in a fibroid should engender suspicion.

CERVICAL CARCINOMA

Approximately 11150 cases of cancer of the uterine cervix were diagnosed in 2007 in the United States. It occurs more frequently in women between the ages of 40 and 60 and more commonly in women of African-American descent than in whites (38). The incidence is only about 2.4 per 100,000 in the United States. In the developing world where it remains one of the leading cancer causes of death among women, the incidence is often five times higher. In the United States at least, the relative incidence of adenocarcinoma and adenosquamous cell carcinoma of the cervix is slowly increasing, relative to the squamous cell type, but the prognosis for these cell types does not seem to be any different than squamous cell carcinoma of the cervix (39). The early detection of cervical cancer by Papanicolaou smear is the most effective means of limiting mortality from cervical cancer (40). Staging of cervical carcinoma relies on size, depth of invasion, and locoregional extent, with no formal incorporation of lymph node involvement for determination of stages I through III. While the International Federation of Gynecology and Obstetrics (FIGO) stage based on size of the primary tumor and compartmental spread of the tumor, carries prognostic significance, each

FIGO stage represents a heterogeneous prognostic group (41). For instance, the addition of chemoradiation to radical surgery for the treatment of patients with early stage cervical cancer when they also have lymph node metastases confined to the pelvis, but not beyond, has led to an improvement of long term survival to 80% in this subset (40). Therefore, the differentiation of those with lymph node involvement confined to the pelvis versus those who have more distant involvement becomes critical to the management of women with cervical cancer. While the standard for the staging of cervical cancer remains the clinical exam, surgical staging plays an increasingly important role (42). In stage IA, which is treated with surgery, and stage IVB, which is treated palliatively, cervical cancer treatment will not likely be altered by additional imaging (41), but for the disease staged in between these, the status of lymph nodes may impact significantly on management. The ability of FDG PET/CT to contribute to staging of lymph nodes, especially para-aortic lymph nodes, has led some to modify treatment on the basis of this new information and, at a minimum, to include para-aortic lymph nodes in radiation fields. Recognition of the importance of distant lymph node metastases to clinical management and prognosis makes PET/CT with FDG an extremely critical tool.

Evaluation of Primary

While pelvic examination under anesthesia remains a standard for staging primary cervical carcinoma, imaging modalities have made an incursion into this. CT has a limited role in assessing primary cervical carcinoma. MRI remains a better means of assessing the extent of corpus uterine involvement by cervical carcinoma and of assessing tumor diameter (Fig. 7) (43). Sensitivity of FDG PET for primary tumors is high but not 100% (44–46). More recently, methods to use FDG PET to determine the size and extent of the primary have been developed. Parametrial involvement is also better assessed by MRI than by FDG PET (46,47) and probably more accurate than examination under anesthesia. In one series, MRI had an 84% accuracy compared with surgical pathology, whereas FIGO staging had a 25% error rate (47). The accuracy of CT alone may be as high as 69% (48) but was exceeded by MRI (90%) for parametrial involvement. Endometrial invasion as assessed by MRI, or by dilatation and curettage, and the size of the tumor predicts positivity in lymph nodes on FDG PET (41,49,50). Similarly, uterine corpus involvement identified on MRI is associated with lymph node involvement (41,50).

The goal of preoperative imaging in cervical cancer is to determine which patients may be suitable candidates for radical hysterectomy. If there is parametrial extension of tumor (stage IIB tumor), radical hysterectomy is contraindicated and the patient is treated with external beam

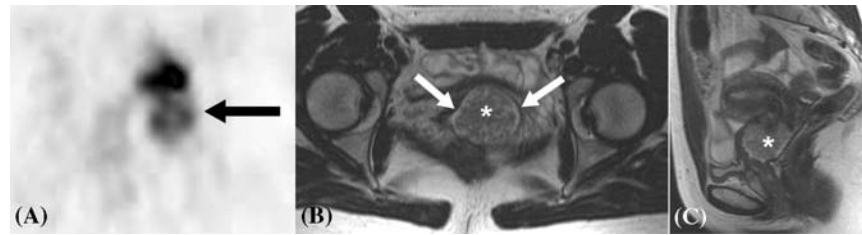


Figure 7 Exophytic primary cervical cancer. (A) Coronal FDG PET performed in a 54-year-old woman with newly diagnosed cervical carcinoma shows increased uptake (*arrow*) corresponding to the exophytic primary tumor seen best on MRI. (B) Axial T2-weighted FSE image demonstrates the high-signal intensity cervical mass (*asterisk*) protruding into the upper portion of the vaginal canal which is expanded around the tumor (*arrows*). (C) The exophytic nature of the tumor (*asterisk*) and vaginal location is best demonstrated on this image obtained in the sagittal plane. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography; FSE, fast spin-echo.

radiation therapy. Therefore, the identification of parametrial invasion is critically important for accurate clinical staging and to direct appropriate therapy. Cross-sectional imaging is best used for evaluation of the primary tumor in clinical stage IB cancer when the primary tumor is greater than 2 cm, since these tumors are associated with significant risk of parametrial and nodal metastases (51). CT has been shown to be more accurate than clinical staging in stage II disease with parametrial involvement and in stage III disease with extension to the pelvic sidewall (52). The goal of CT in the primary evaluation of cervical cancer is to differentiate confined tumor from parametrial extension, evaluate for lymph node metastases, and screen for organ invasion and metastases in stages IIB–IVB tumor (Fig. 8). However, limitations of CT are overstaging of IB tumors because of misinterpretation of normal parametrial structures as extrauterine spread of the disease, understaging IIB–IIIB tumors because of microscopic local tumor spread, difficulty in confirming bladder or rectal invasion unless tumor has penetrated through the serosa and muscularis, inability to detect tumor in lymph nodes less than 1.5 cm, and false-positive diagnoses of enlarged lymph nodes due to reactive hyperplasia, chronic lymphadenitis, or fatty replacement (34). In general, the accuracy of CT in local staging of cervical carcinoma is limited (53). CT is not well suited to evaluate tumor size or stromal invasion due to low accuracy in distinguishing a tumor from surrounding normal cervical tissue (48). In identifying parametrial involvement, CT has an accuracy of 55% to 70% and the overall staging accuracy is as low as 45% to 63% (48,54).

In contrast, the superior contrast resolution of MRI makes it an ideal imaging modality for evaluating cervical carcinoma (Fig. 7). Cervical carcinoma appears as a high-signal intensity mass on T2-weighted images in the background of the low-signal intensity cervical stroma, with variable contrast enhancement after gadolinium administration. Excellent contrast resolution between tumor and normal cervical tissue allows for more accurate

measurements of tumor size as well as improved detection or exclusion of parametrial spread and overall tumor staging (53). MRI has been shown to be up to 93% accurate in measuring tumor size to within 5 mm of measurements obtained from surgical specimens (48,55,56). In a comparative study of CT and MRI by Subak et al. (48), MRI was shown to be better than CT in demonstrating tumor size and stromal invasion with an overall staging accuracy for MRI of 90% compared with 65% for CT. CT and MRI were comparable in assessing lymphadenopathy. Similar findings were shown by Kim et al. (54). Therefore, MRI is widely considered the imaging method of choice to initially stage patients with clinically suspected invasive cervical carcinoma.

Because of the above-described limitations, the current role of CT in the imaging of cervical cancer is mainly for the staging of advanced tumors and evaluating patients for tumor recurrence. However, most studies evaluating the accuracy of CT for staging cervical cancer were performed using earlier generation CT scanners, and without optimized contrast enhancement. (34,54,57,58). The major limitation of CT is partial volume averaging which blurs the planes between the uterus, bladder, and bowel (7). Major advances in CT technology with the availability of MDCT scanners may broaden its use in imaging of cervical cancer (59). Increase in the number of detector rows in scanners allows for simultaneous acquisition of multiple slices with reduced slice thickness, thereby, increasing spatial resolution. With these thin slices, multiplanar images can be reconstructed, which may lead to improved staging of local tumor extension.

Most recently, data from the Intergroup Study American College of Radiology Imaging Network—Gynecologic Oncology Group Trial assessing the role of imaging in pretreatment evaluation of early invasive cervical cancer have become available (51). This was a multicenter study comparing by FIGO clinical staging with MRI and CT using surgicopathologic findings as the reference standard. This assessment showed lower-staging accuracy of both CT

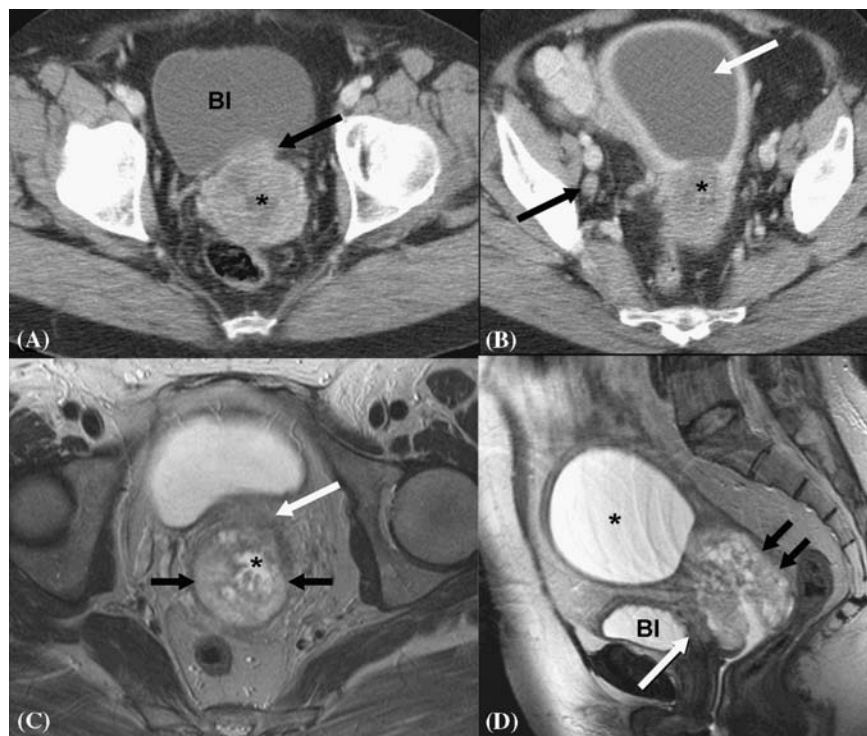


Figure 8 Primary cervical cancer, stage IV. (A) Axial CT demonstrates bulky cervical mass (*asterisk*). There is loss of fat plane between cervix and posterior bladder wall, suspicious for bladder invasion (*arrow*). Assessment is limited on this axial scan. (B) Slightly more superior image demonstrates the cervical mass (*asterisk*). There is obstruction of the uterine cavity, which is markedly distended and fluid-filled (*white arrow*). Enlarged right pelvic sidewall lymph node is also present (*black arrow*). (C) Axial T2-weighted FSE image demonstrates intermediate signal-intensity cervical mass (*asterisk*) with high-signal intensity fluid located centrally within the endocervical canal. The low-signal intensity cervical stromal ring (*black arrows*) is disrupted on the left (*white arrow*), consistent with parametrial tumor extension. There is also extension of tumor to the posterior bladder wall. (D) Sagittal T2-weighted FSE MR image again demonstrates the cervical mass (*black arrows*) and large amount of high-signal intensity fluid within the markedly distended endometrial cavity (*asterisk*). Extension of tumor to the posterior wall of the urinary bladder is best demonstrated on this plane (*white arrow*). Abbreviations: BI, urinary bladder; FSE, fast spin-echo.

and MRI compared with earlier studies. For stage IIB or higher disease, the sensitivities were 53% for MRI and 42% for CT. In this study, MRI was superior for detection of tumor and localization but there was no statistically significant difference between MRI and CT for overall staging. The use of helical CT technology with thinner collimation and higher table speed per rotation may explain the improved results for CT compared with earlier studies. Further studies are needed to determine if MDCT technology will allow for improved detection and staging of cervical carcinoma.

At CT, early cervical cancer may appear as a cervical mass with areas of low attenuation because of necrosis, ulceration, or reduced vascularity (7). Cervical carcinoma is typically hypoattenuating on contrast-enhanced CT because of decreased vascularity compared with the cervical stroma; therefore, IV contrast administration is critical when performing CT to evaluate cervical cancer (Fig. 8). However, up to 50% of stage IB tumors are

described as undetectable since they are isodense with the normal cervical parenchyma (59). With more advanced disease (Fig. 9), the cervix is enlarged to greater than 3.5 cm in anterior to posterior dimension, and a cervical size greater than 6 cm correlates with a poorer outcome (60,61) (Table 2). Invasion of the myometrium and vaginal extension, as well as the superior and inferior extent of the tumor may be better determined on reformatted sagittal and coronal images (Figs. 7, 8) (59).

CT findings of parametrial tumor invasion (stage IIB) are explained in Table 3. It is important not to mistake the normal cardinal ligament or normal parametrial vessels as parametrial tumor extension. Inflammatory changes around the cervix resulting from recent intervention may also be misinterpreted as tumor. Therefore, for parametrial invasion to be diagnosed, there must be a soft tissue mass with infiltration rather than ill-defined edema in the parametrial tissues (62). Invasion of the pelvic sidewall appears as a heterogeneous mass extending to the

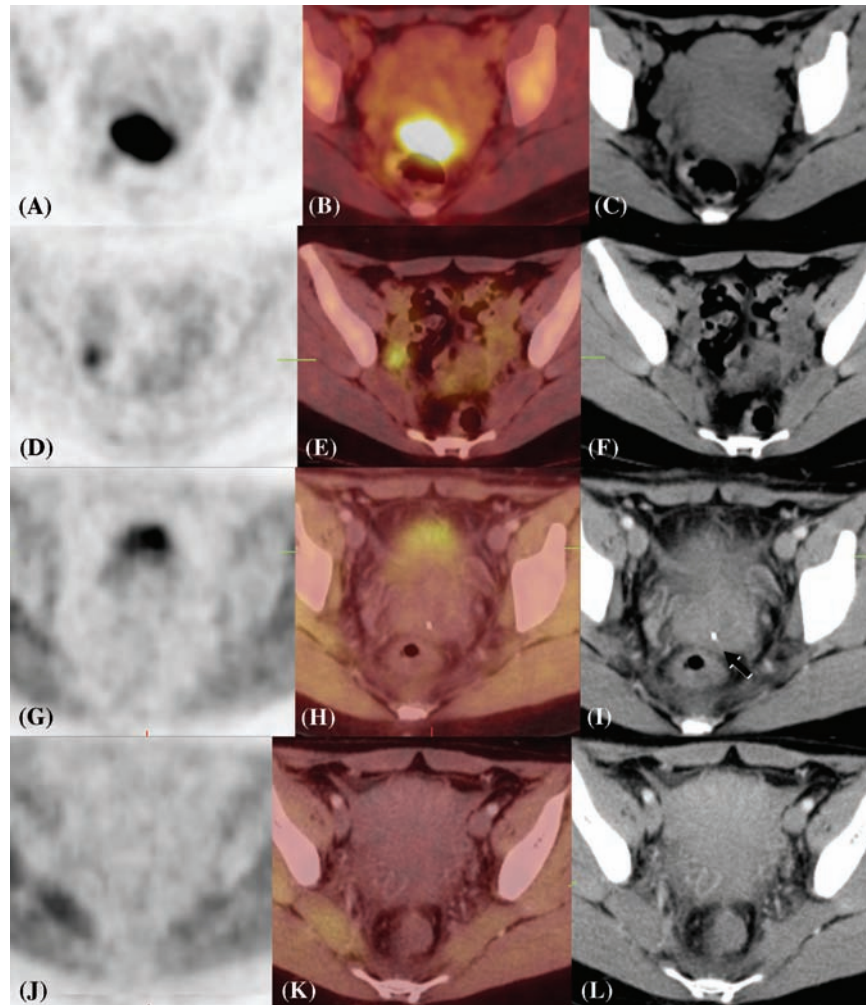


Figure 9 Primary cervical pre and post. PET/CT performed prior to therapy in a 26-year-old woman with newly diagnosed stage IIb cervical cancer. Intense uptake is seen on the FDG PET images (A) fusing (B) to the cervical mass on CT (C). At a slice at a slightly more cephalad level uptake on PET (D) fuses (E) to a right pelvic sidewall lymph node on CT (F). The patient underwent chemotherapy and brachytherapy, all of which was completed two months prior to the follow up PET/CT. At follow up the FDG PET (G) shows resolution of the tumor activity. The fused PET/ CT (H) and the CT (I) slice show the radiation seed implant in the middle of the persistent mass. There has also been resolution of the metabolic activity (J) associated with the previously seen lymphadenopathy. The lymph node has also resolved on both the fused (K) and CT (L) images. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography.

Table 2 Cervical Carcinoma: CT Findings

Cervix enlarged to greater than 3.5 cm in anterior to posterior dimension (>6 cm poorer outcome (60,111)
Obstruction of the uterus with distention of the endometrial cavity with blood and secretions
Invasion of the myometrium
Vaginal extension (59)

obturator internus or piriformis muscle. At CT, invasion of the pelvic sidewall is diagnosed when the tumor is located less than 3 mm from the sidewall (63). Obstruction of the ureter or enlarged pelvic lymph nodes indicate stage IIIB

Table 3 CT Findings of Parametrial Invasion by Cervical Carcinoma

Irregularity or poor definition of the lateral cervical margins
Prominent parametrial soft tissue strands
Increased density or mass around the pelvic ureter
Presence of an eccentric soft tissue mass

disease (Fig. 8). Cervical cancer then spreads along the iliac nodal chains and to the para-aortic lymph nodes (64).

Stage IV carcinoma occurs when there is bladder or rectal invasion (Fig. 8). CT criteria for bladder or rectal involvement include focal loss of the perivesical/perirectal fat plane

accompanied by asymmetric wall thickening, nodular indentations or serrations along the bladder/rectal wall, intraluminal tumor or mass, and vesicovaginal fistula (34).

Characteristics of the Primary Tumor

Tumor volume is an important prognostic indicator in the management of cervical cancer. Clinical estimation of tumor size correlates poorly with tumor volume (56). At CT, inability to discriminate between tumor and normal tissue also limits accuracy in determining the tumor volume (54). Because of inherent better soft tissue contrast, MRI can more reliably distinguish cervical tumor from surrounding normal tissue, and this modality allows for the most accurate determination of tumor volume. Narayan et al. (43) demonstrated that in patients with FIGO stage I or II disease, pathologic tumor diameter correlated well with the corresponding MRI diameter, as measured on T2-weighted images. However, as discussed previously, CT tumor volume measurement may be more accurate with MDCT technology, and this needs further study.

On FDG PET high SUV of the primary tumor does not predict lymph node involvement, clinical stage, or size of the tumor (Fig. 9) (44,45,65), but SUV may be a prognostic indicator. Xue et al. (45) found that patients with less than the median SUV in their series (<10.2) had a significantly increased five-year disease-free survival compared with those with SUVs greater than 10.2. Overall survival was not significantly different. Nonetheless, the absolute cutoff for SUV to predict outcome has not been established. But in that series of patients treated with radiation with or without concurrent chemotherapy, both low SUV and FIGO stage I showed a predictive value for longer disease-free survival (45).

Lymph Nodes

Lymph nodes that measure greater than 1 cm in short-axis dimension on CT are considered abnormal (Fig. 9) (66). Upper limits normal for individual nodal groups in the pelvis are 7 mm for the internal iliac nodes, 9 mm for the common iliac nodes, and 10 mm for the external iliac nodes (67). Retroperitoneal lymph nodes 10 mm or larger are considered highly suspicious for metastatic disease outside of the pelvis (Stage IVB). The presence of pelvic or para-aortic lymph node metastasis excludes surgery in patients with cervical cancer. Therefore, accurate lymph node staging is critical in determining appropriate therapy. CT and MRI perform equally well in the assessment of pelvic and para-aortic lymph node metastasis with an accuracy of 86% to 93% (48,53). A comparative meta-analysis between lymphangiography, CT, and MRI showed MRI to be slightly better than lymphangiography, and that CT and MRI were not significantly different (66).

The use of lymphangiography is no longer advocated. The determination of metastatic infiltration of lymph nodes by CT or MRI is based on nodal size. As stated above, most authors use a diameter of greater than 1 cm as the threshold for metastatic lymph node involvement, achieving high accuracy (68–71). However, using this criterion, specificity is greater than sensitivity, with CT achieving a specificity of up to 93% versus a sensitivity of up to 44% for nodal involvement (48,72–74). At MRI, using a minimal axial diameter of greater than 1 cm as evidence of metastatic involvement, Kim et al. found a sensitivity of 62%, specificity of 98% and an accuracy of 93% (75). Another important finding associated with metastatic involvement is the presence of central necrosis in the node on contrast-enhanced CT (76). With a minimal axial diameter of greater than 1 cm as evidence of metastatic involvement, Kim et al. found a sensitivity of 62%, specificity of 98%, and an accuracy of 93%. An additional important finding associated with metastatic involvement which may improve the accuracy of lymph node staging is the presence of central necrosis in the node on contrast-enhanced imaging (76). The limitations of both CT and MRI in nodal staging include inability to recognize tumor in normal-sized or small nodes and inability to differentiate between large, nonmetastatic, reactive nodes, and metastatic involvement.

Adding PET to CT increases the sensitivity. The sensitivity of FDG PET or PET/CT for lymph node metastases increases with the clinical stage and the size of the primary tumor (49) as does the incidence of lymph node metastases. Patients with endometrial invasion are more likely to show positive FDG PET in lymph nodes, although tumor size has not always been shown to correlate with lymph node status (77). In a study of early clinical stage cervical cancers, IA2 to IIA, FDG PET alone showed a low sensitivity (10%) for the detection of lymph node metastases in the pelvis, likely due to the small size of the metastatic deposits (78).

As the size of the metastatic implants increases, sensitivity of PET increases. In one series of patients with a similar clinical stage, patients with a larger metastatic tumor burden (15.2 mm vs. 6 mm) and a higher prevalence of positive lymph nodes at surgery (32% vs. 16.7%), the sensitivity of PET per lesion increased to 46%. Sensitivity on a per patient basis was 53%. Specificity in the patients with greater tumor burden was also higher at 90% on a per patient basis and 91% on a per lesion basis (79). Size of metastatic lymph node deposits bears directly on PET sensitivity. Roh et al. stratified the lymph node metastases in their patients and found a 52% sensitivity for metastases greater than 5 mm that increased to 65% for metastases greater than 10 mm with an overall sensitivity of almost 38% (80). In their subjects, MRI shows a 32% sensitivity overall increasing to almost 43% in metastases

greater than 5 mm and 54.5% in metastases greater than 10 mm. In a series performed with PET/CT, sensitivity increased from 72% to 100% for lymph nodes greater than 5 mm (71).

Most patients with para-aortic lymph node involvement also have pelvic lymph node involvement on FDG PET (49). In the study by Wright et al. (79), 9% of patients who underwent para-aortic sampling had lymph node metastases. While specificity was 98%, sensitivity was only 25% on a per patient basis, but PET did detect 40% of the lymph node metastases (79). While CT detected only 12% of the lymph node metastases compared with 26% by FDG PET in a head-to-head comparison, the combination detected 67%. The increased sensitivity of FDG PET relative to MRI or CT has been shown by others as well (44). But this increased sensitivity underscores the potential of PET/CT for this purpose.

PET/CT has shown a sensitivity of 60% for lymph nodes, but a very high specificity of 94% in a series of patients with a range of cervical stages I–IV, but with a large number of early stage (I) patients. The dedicated PET/CT offered additional information in 43% of the patients over PET or CT alone (81). In another similar group of patients, PET/CT showed comparable sensitivity and was significantly more sensitive than MRI with comparable specificity and a trend toward greater accuracy (82). On a per patient basis, sensitivity of PET/CT increased to 77%. In a group of early stage patients (IA and IB), the sensitivity of PET/CT was 72% on a per lymph node basis and 73% on a per patient basis (71).

While lymph node involvement does not come into FIGO staging, a number of authors have now shown the independent prognostic significance of lymph node positivity. In spite of its imperfect sensitivity of PET/CT, the larger the size of the involved lymph nodes, the more PET positivity appears to impact on overall prognosis. Patients with lymph nodes greater than 10 mm in size on CT more often have cervical cancer-associated mortality (32.6%) and recurrence with distant metastases than patients with lymph nodes smaller than 5 mm (83). In a group of patients treated with chemoradiation, those with PET negative para-aortic lymph nodes had significantly improved overall survival (84) and progression-free survival (85) compared with patients with positive para-aortic lymph nodes for all stages. This progression-free survival was found even when the para-aortic lymph nodes were included in the radiation field. Most of these patients recurred distantly. Interestingly, PET-positive para-aortic nodes smaller than 1 cm had the same implications for survival, as did lymph nodes greater than 1 cm on CT. Positivity by any criterion in para-aortic lymph nodes implied a worse prognosis. In the pelvis, though PET-positive lymph nodes were associated with a worse prognosis only when lymph nodes reached greater than

2 cm and in patients with stage IB disease. Thus, the location and presence of PET-positive lymph nodes at diagnosis predicted recurrent disease. When PET/CT combined indicates extracervical disease, a significant decrease in disease-free survival is found as well (81).

More distant lymph node uptake is less frequently seen, but is the most common site of distant metastasis and may imply a much worse outcome. FDG identification of supraclavicular lymph nodes appears to identify tumors with genetic characteristics that may carry a worse prognosis (86). Sensitivity and specificity for distant nodal disease is high (3). Extranodal uptake, however, at least on PET alone, is more likely to be false positive for metastases (44).

Treatment Decisions

The introduction of FDG PET into the staging algorithm can alter treatment (87). In a small series of patients, Unger et al. (46) suggested that the PPV of PET for pelvic lymph node involvement could be used to select chemoradiation over radical surgery (Fig. 9). Others have suggested that higher doses of radiation should be directed selectively at PET/CT positive lymph nodes instead of directing a high dose uniformly to nodal beds, thereby avoiding some of the associated morbidity (88). Techniques like intensity-modulated radiation therapy and proton therapy now make this possible. A change in radiation treatment fields in response to positive para-aortic lymph nodes whether on PET, or MRI, or CT may improve survival (44). Failure within the radiation field is much less likely, although patients are at risk for distant recurrence when positive para-aortic lymph nodes are treated (44,84).

Treatment Planning

Brachytherapy or external beam radiotherapy is used in the treatment of stage IIB, III, and IV cervical cancer. CT may be used to evaluate tumor extent for radiation therapy planning, and determine radiation therapy portals as well as detect complications of radiation such as uterine perforation, rectovesical fistula, sigmoiditis, rectal stricture, urethral stricture, and sacral insufficiency fractures (7,89). Findings at CT may also be helpful in predicting complications of radiation therapy. Findings show that a thinner anterior lower uterine wall correlates with increased late bladder and ureteral toxicity, and a thinner anterior upper uterine wall correlates with increased late small bowel toxicity (90).

Effect on Radiation Port

Changes in radiation treatment volumes and dose may occur with the incorporation of PET metabolic information into the planning CT, although typically CT is used

for determining treatment volume. Methodology to apply the FDG PET information to determining treatment volume has been developed. By thresholding the PET image at 40% of tumor maximum SUV, delineation of the tumor boundary on the PET information can be made accurately (6,77,91). PET determinations of tumor volume correlate well with FIGO stage with conventional methodology (77). The use of metabolic 3D planning for brachytherapy may provide better information about dose to bladder and rectum as well as the extent and dose intensity to tumor. Studies of FDG PET alone with radiotracer-filled applicators have been used to determine the potentially achievable 3D treatment volume from high dose rate brachytherapy in combination with intensity-modulated external radiation treatment. With that technique minimum doses to tumors increased and improved tumor coverage (4). Although doses to the rectum were not significantly altered, the dose to the bladder was significantly decreased with this method. Difficulty with using PET information without CT in that study would be eliminated by dedicated PET/CT. The possibility of repeat assessments of brachytherapy plans as tumors undergo treatment response could improve efficacy (6). The inclusion of metabolic information altered determinations of gross tumor volume in radiation treatment plans in a significant number of patients by as much as 25% (92). PET-guided intensity-modulated radiation treatment plans theoretically allows higher doses to para-aortic lymph nodes by close to 30% without added toxicity to normal organs (93,94). The metabolic images can also be used to follow the interim changes in tumor volume in response to radiation treatment which provides important prognostic prediction in terms of both local recurrence and overall survival (91).

Radiation Therapy Effects

A limitation of both CT and MRI is the differentiation of radiation induced or postsurgical fibrosis from recurrent pelvic tumor. Vesicovaginal and or rectovaginal fistulae may also result from radiation therapy, which may be assessed by fluoroscopic studies. The more distinctive CT findings of pelvic recurrent tumor are asymmetry with the presence of a soft tissue mass with hypodense tumor foci, compression, and invasion of normal adjacent organs, and mass extension to involve the pelvic sidewall, iliopsoas muscle, or bone (34). Radiation-induced changes (Fig. 9) include poor definition and irregularity of the parametria without pelvic sidewall disease extension, thickening of the perirectal fascia, widening of the presacral space, and thick-walled bladder, and the rectum (95). Additional changes include diffuse increase in density of the posterior pelvic fat and thickening of small bowel loops (34). Biopsy may be necessary to differentiate recurrent tumor

from these fibrotic changes. Contrast-enhanced MRI has a reported accuracy of 82% to 83% in this setting (96,97).

PET Appearance

In FDG PET, the appearance of intense uptake superimposed on the vaginal cuff is indicative of recurrence. This uptake, combined with changes in CT soft tissue appearance, increases the index of suspicion significantly. Adjacent rectal or bladder activity can be problematic, however, even with in-line PET/CT. Sometimes, a post-void acquisition may be helpful.

The differentiation from radiation change may also be difficult. When adjacent bowel shows diffusely increased uptake within the field, the possibility of radiation change must be considered even four to five months after the end of therapy (98). Knowledge of specific postradiation symptoms and complications may eliminate the false positive because of inflammation or even sequelae like fistulas.

Surveillance

Posttherapy surveillance of patients treated for primary cervical cancer consists of frequent physical examination, Papanicolaou smear, chest radiographs, and testing for squamous cell cancer (SCC) antigen (99). FDG PET should be used after neoadjuvant therapy and also after curative intent therapy for surveillance for recurrence. The sensitivity of FDG PET for locally recurrent primary tumors ranges from 90% to 100% and generally exceeds that of CT or MRI. In a small series of patients, FDG PET distinguished local recurrence from distant recurrence accurately (3). Specificity has not been found to be as high (100). Focal rectal uptake and radiation change can both cause false positives (3). PET/CT would be expected to eliminate the false positives because of rectal uptake, although it may not be as helpful with radiation change.

The yield of positive PET scans increases in patient with symptoms to about 67%, but even in asymptomatic patients, the detection rate has approached 31% (99,101) although lower yields of positive PET scans in asymptomatic patients have been reported (5) (Fig. 10). With elevated serum SCC, PET has yielded a 94% detection rate (102) and shortened the time interval usually encountered between detection of the tumor marker and identification of the tumor (102). Although sensitivity may approach 90% (100,101,103), specificity for recurrence is hampered in the setting of radiation changes such as colitis and fistula formation (103). Patients without serum marker elevations may be more likely to have localized disease amenable to surgical salvage. In those patients, early detection with PET may make the difference between curative salvage therapy and succumbing to the disease (104). Even in asymptomatic patients with

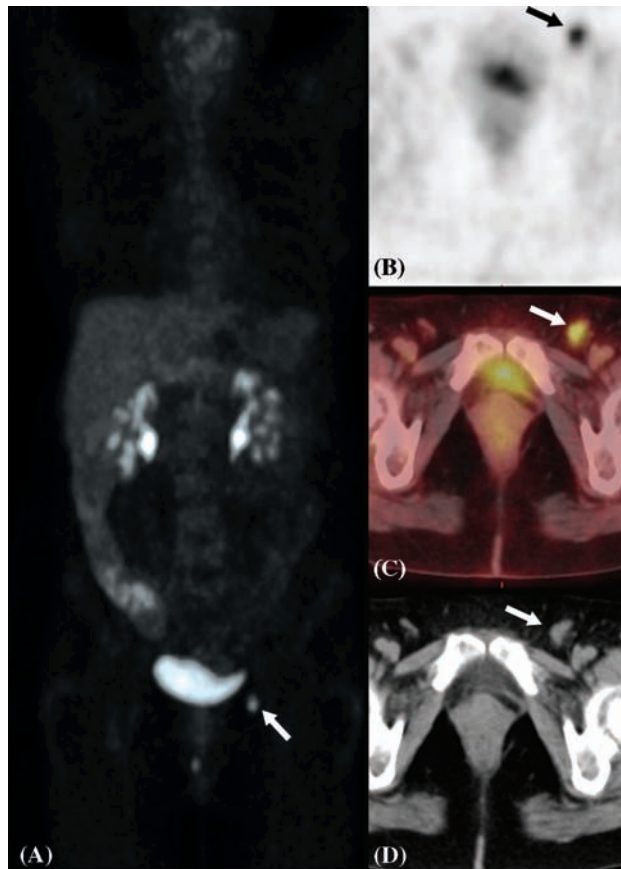


Figure 10 Recurrent cervical carcinoma. Anterior view of an MIP from the FDG PET images of the (PET/CT (A) show the single focus of uptake at the left inguinal region (arrow). Images of the pelvis showed only the unremarkable vaginal cuff. The transaxial PET slice (B), the fused image (C), and the corresponding CT slice (D) show the involved lymph node (arrows) which was the only site of recurrence in the 39-year-old woman previously treated with chemotherapy and brachytherapy for cervical carcinoma. *Abbreviations:* FDG, fluorodeoxyglucose; MIP, maximum intensity projection; PET, positron emission tomography.

negative markers, the sensitivity for disease was greater than 80%. Possibly more important, the NPV was 100%. Thus, even without evidence of recurrence, FDG PET may prove to be a sensitive and important surveillance tool.

Recurrence

In patients with pelvic recurrence, surgery may suffice for salvage therapy, but once the disease recurs in multiple sites or distantly, palliative therapy is indicated (Fig. 11). Thus, early detection of recurrence, when it may be limited to the pelvis, could improve survival. When the disease is found beyond the pelvis, the morbidity of curative intent salvage therapy can be avoided. FDG

PET, especially in concert with CT, can provide more sensitive staging at recurrence than morphologic imaging alone [91% vs. 67% in one series (105)]. In another series, the FDG PET finding was positive in all patients who had abnormal serum tumor markers and abnormal in those who also showed some evidence of recurrence on another imaging modality (100). Even in asymptomatic women, FDG PET alone detected recurrence in 80% with a 100% PPV (99). In a review of the literature, sensitivities of FDG PET for recurrence range from 86% to 100% with specificities from 60% to 98% and reported accuracies from 70% to 97% (106). Recurrent disease on FDG PET has prognostic significance (5). In one series, treatment was changed in over half the patients after FDG PET. In about two-thirds of those patients, a curative treatment plan was changed to palliation (105). Inclusion of FDG PET has resulted in much better survival of patients in whom surgical salvage with curative intent is used than when PET is not included in the assessment, suggesting that the addition of PET results in better selection of patients (102,104).

Vaginal Cuff

Pelvic recurrence of cervical cancer may occur centrally in the preserved cervix or in the postsurgical bed or vaginal cuff (Fig. 11) (107). As in the evaluation of the primary tumor, MRI may be superior to CT because of high contrast resolution and the ability to demonstrate the cervical zonal anatomy (108,109). Residual tumor has high-signal intensity on T2-weighted images, similar to the primary tumor. CT is significantly more accurate in assessing recurrent cervical cancer than in initial tumor staging (110,111). Serial CT scans provide an objective measurement of tumor response to radiation or chemotherapy in nonsurgical candidates. Pelvic CT performed six weeks after completion of radiation therapy is helpful as a baseline for follow-up (62). Fibrotic pelvic soft tissues masses and thickening of the uterosacral ligaments may result from radiation and may simulate recurrent disease.

The CT and MRI appearances of the central pelvis are similar after radical hysterectomy. The vaginal fornix typically forms a linear soft-tissue configuration (112). Recurrent tumor in the cervix will appear as enlargement and heterogeneous contrast enhancement. Obstruction of the cervical os may result in hydrometra. Recurrence at the vaginal cuff will appear as a soft tissue mass arising in the cuff. If the mass contains air, this finding suggests the presence of a rectovaginal fistula. This finding can be confirmed with contrast enema to demonstrate the fistulous communication. There may also be a direct spread to the urinary bladder anteriorly or the anterior abdominal wall. Vesicovaginal fistula may be demonstrated on a CT scan performed after IV contrast, if the images are

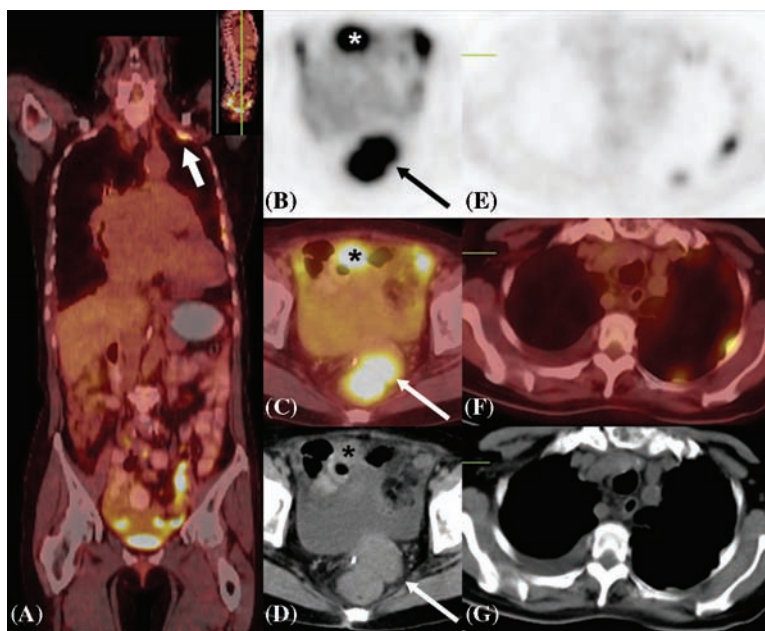


Figure 11 Metastatic cervical carcinoma. Coronal fused slice from (an FDG PET/CT (A) shows uptake in the pelvis and in addition focally increased uptake at the left pleura (*arrow*). Corresponding transaxial slices from the PET (B), fused image set (C) and CT (D) show the vaginal cuff recurrence (*arrow*) as well as physiologic uptake in normal bowel (*asterisk*), and a left external iliac lymph node. In addition, corresponding transaxial slices through the thorax from the PET (E), fused image sets (F), and CT (G) show metabolically active left sided pleural metastases in this 54-year-old woman with a history of squamous cell cervical carcinoma treated with curative intent five years earlier. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography.

performed during the excretory phase with contrast opacification of the urinary bladder. There may be hydronephrosis secondary to ureteral involvement. Both CT and MRI play an important role in the early detection of recurrent nodal disease.

Distant Disease

FDG PET restaging of lymph nodes has been shown to have 92% to 100% sensitivity, higher than either CT or MRI (60%) in patients with recurrent disease (100,101,105). Sensitivity of FDG PET alone is especially high in distant lymph nodes (e.g., scalene and mediastinal nodes) but was lower in pelvic nodes. Presumably the addition of CT to PET would improve the detection of para-aortic lymph nodes in the setting of recurrence and, possibly, in the detection of retrovesical lymph nodes that can be problematic on PET alone. The differentiation of lymph nodes from the ureter and bowel using the fused CT and the recognition of mild activity in small lymph nodes on PET/CT would contribute to this improvement. Specificity in one group of patients was moderately high, 76% (101).

Visceral Metastases

Liver metastases occur in one-third of patients who present with recurrent cervical carcinoma (113) and will

appear as focal low attenuation lesions. Adrenal metastases occur in 14% to 16% patients (113). These occur more frequently with adenocarcinoma than with squamous cell carcinomas. The spleen, pancreas, and kidneys are rarely involved by metastatic disease. Other sites of recurrence include the peritoneum, omentum, and mesentery. The rectum is frequently involved by recurrent cervical carcinoma, as a result of contiguous extension from the cervix or vaginal cuff. Invasion typically occurs at the level of the rectosigmoid junction. Lung metastases occur in 33% to 38% and osseous metastases in 15% to 29% (107).

Cervical cancer metastases to the liver, pleura, bone, and lung have been detected with FDG PET alone (100–102). The sensitivity of FDG PET for lung metastases is relatively low compared with CT; small nodules will likely only be detected by CT (100). While the CT scan performed in the context of PET/CT may be less sensitive than diagnostic chest CT, it is likely that this scan will improve the ability to detect small metastatic pulmonary nodules.

Treatment Response

Limited studies are available concerning the use of PET for monitoring response to therapy. In patients undergoing neoadjuvant chemotherapy, a decrease in SUV has been associated with a positive histologic response (114). In the

midst of radiation therapy, changes in PET-derived tumor volumes have been documented and incorporated into radiation treatment plans. Postradiation therapy PET likely has prognostic significance (Fig. 10). In a group of patients treated with external beam radiation and brachytherapy, those patients without abnormal FDG uptake had a five-year survival estimate of 80%. Those with persistent uptake had a five-year survival of 32%, and for those with new sites of uptake outside the radiation field, the five-year survival was 0% (115). Three months after chemoradiation therapy, residual FDG activity in the cervix was associated with a 0% five-year disease-free survival compared with 83% in those without activity (91).

OVARIAN CARCINOMA

Most patients with ovarian carcinoma present with stage IV disease, but occasionally an adnexal mass will be found incidentally on PET/CT in women being scanned for other reasons (Fig. 3). Although it must be differentiated from a benign cause in premenopausal women, in the postmenopausal patient, intense uptake in an ovary should be suspect (24). In addition, on the basis of the work of Lerman et al., an SUV of greater than 7.9 should also raise suspicions of malignancy (24). While metastases with certain primaries [breast (116,117) and gastroin-

testinal primary tumors] occur, primary ovarian cancer should also be a consideration. It should be noted that tumors of low malignant potential and pT1a cystadenocarcinoma do not demonstrate significant uptake on FDG PET (Fig. 4) (116). Not surprisingly, FDG uptake in ovarian tumors had been associated with markers of proliferation and with histologic grade (Fig. 12) (118). Comparing US and MRI with PET alone in a group of women with adnexal masses suspicious for malignancy on the basis of clinical presentation, sensitivities were 92% (US), 83% (MRI), and 58% (FDG PET). Specificities were 60%, 84%, and 76%, respectively. The combination of all three, however, improved to 92% sensitivity with no loss in specificity 85% (116). The prevalence of malignancy in that series was 12%. In another series of patients presenting with pelvic masses identified on US, where malignancy was present in 60%, PET had a sensitivity of 58% compared with an MRI sensitivity of 91%. Combined, the sensitivity was still 91% and specificity was unchanged at 87% for PET alone, MRI alone, and the combination (119). Certainly, PET is not an adequate screening tool for adnexal masses, but it may add to the evaluation of adnexal masses.

US is considered the first-line imaging modality of choice for evaluation of a clinically suspected adnexal mass. US findings that suggest malignancy are: multilocularity, thick septations, a large soft-tissue component

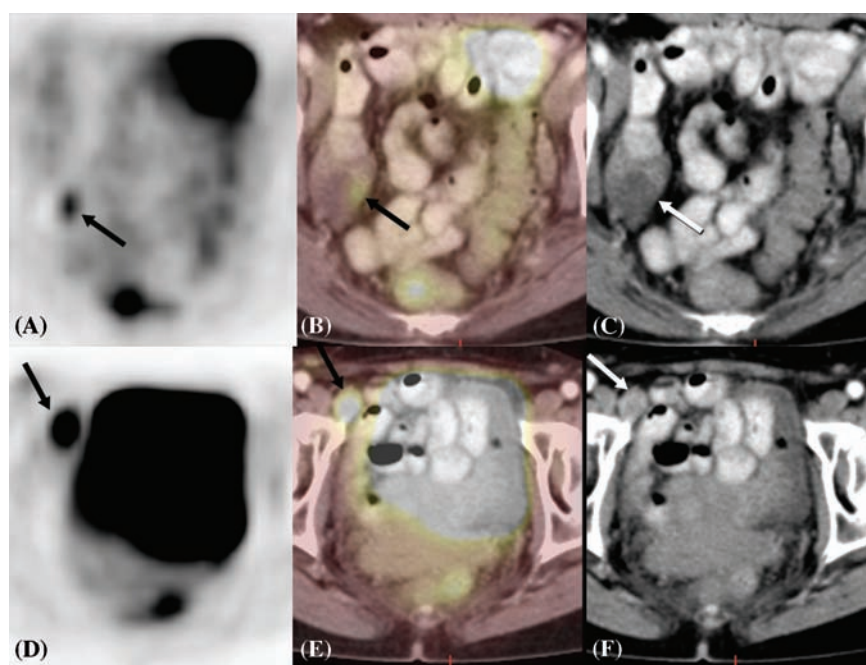


Figure 12 Carcinosarcoma of the ovary. A small focus of increased uptake is seen fusing to the medial aspect of the right ovary (arrow) (A–C) in this woman who had otherwise had a good response to chemotherapy for her non-Hodgkin’s lymphoma. At surgery, this was found to be a high-grade carcinosarcoma (mixed Mullerian tumor). (D–F) At the same examination, a newly active right external iliac lymph node was identified on PET and CT (arrow). Abbreviation: PET, positron emission tomography.

with vascularity at color Doppler, and papillary projections. MRI can also serve a very useful problem-solving role in further characterization of the problematic adnexal mass when US findings are not definitive. At CT, there may be considerable overlap between the appearance of ovarian cancer and complex benign ovarian cysts. However, worrisome CT findings include a multilocular cyst with thick septations and solid mural or septal components, a partially cystic and solid mass, and a lobulated papillary mass (18). At CT, it may not be possible to differentiate between solid components and areas of hemorrhage unless pre and postcontrast images are acquired. The main role of CT in ovarian cancer is in the staging and the detection of extraovarian disease.

However, in patients presenting with paraneoplastic neurologic symptoms, FDG PET has played a role in detecting the location of the primary, sometimes by identifying involved regional lymph nodes or other metastases rather than identifying the primary tumor itself. In ovarian cancer, these syndromes are associated with the generation of anti-Yo antibodies (117,120). The sensitivity of PET for malignancy increased with peritoneal spread of disease in those patients.

Staging of Ovarian Cancer and Detection of Recurrent Cancer

Most patients with ovarian cancer present with stages III or IV of the disease and generally undergo staging laparotomy with tumor debulking. Preliminary staging with imaging may help to identify those patients who may not be amenable to primary surgical debulking and may be better served by neoadjuvant chemotherapy. One

of the most important prognostic factors in epithelial ovarian cancer is the volume of disease that remains after surgical cytoreduction (121). There is a survival advantage if patients undergo “optimal” surgical debulking which, according to the Gynecologic Oncology Group (GOG), includes residual disease less than 1 cm. Patients thought to have the disease, but not amenable to optimal cytoreduction, can be offered neoadjuvant chemotherapy with surgical debulking at a later date. Bulky disease in the upper abdomen involving the diaphragms, liver, porta hepatic, spleen or suprarenal lymph nodes are often the reason that optimal cytoreduction may not be achieved (122,123). Knowledge of disease at these and other sites is useful for surgical planning.

Ovarian cancer spreads by several routes, including direct extension to surrounding pelvic organs and the pelvic sidewalls, intraperitoneal implantation, lymphatic, and hematogenous spread. Peritoneal spread is the primary mode of spread of ovarian cancer and occurs by exfoliation of malignant cells, which then follow the normal circulation of peritoneal fluid and implant and grow as surface nodules. Common sites of intraperitoneal seeding include the omentum, paracolic gutters, liver capsule, and diaphragm (8,124,125). Peritoneal implants are soft tissue masses that may appear as solitary or multiple nodules (Fig. 13). These nodules may coalesce to form plaques that coat the viscera and appear as areas of irregular soft-tissue thickening (126). There may be soft tissue infiltration of the omental fat or formation of discrete nodules with large omental plaques referred to as omental cakes. Peritoneal implants may calcify or may be low attenuation and mimic loculated fluid (8). Implants on the diaphragmatic surface appear as nodular or

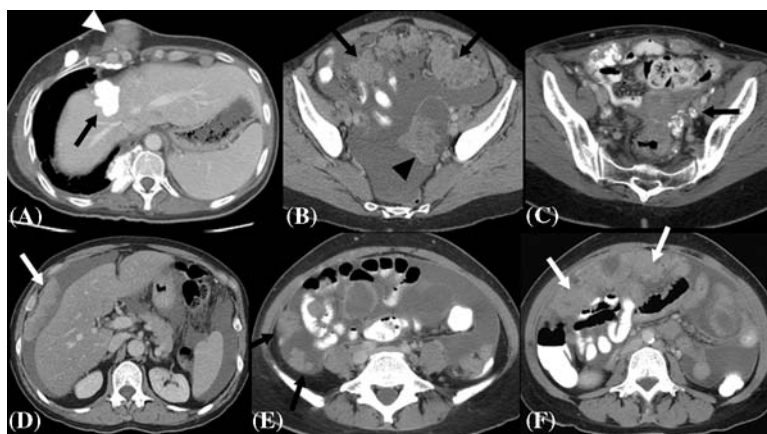


Figure 13 CT of peritoneal carcinomatosis. Several patients with peritoneal carcinomatosis secondary to metastatic ovarian carcinoma; (A) calcified implant at the dome of the liver (arrow) and implant in the anterior abdominal wall (arrowhead); (B) Extensive soft-tissue infiltration of the greater omentum in the pelvis (omental caking, arrows). Left pelvic sidewall implant (arrowhead) appearing as solid and cystic mass. (C) Partially calcified left pelvic side-wall implant (arrow). (D) Peritoneal tumor implant is located anterior to the right lobe of the liver (arrow). Ascites fluid is also present. (E) Tumor implants in the paracolic gutters (arrows) as well as ascites fluid. (F) Tumor infiltration of the greater omentum (omental caking, arrows).

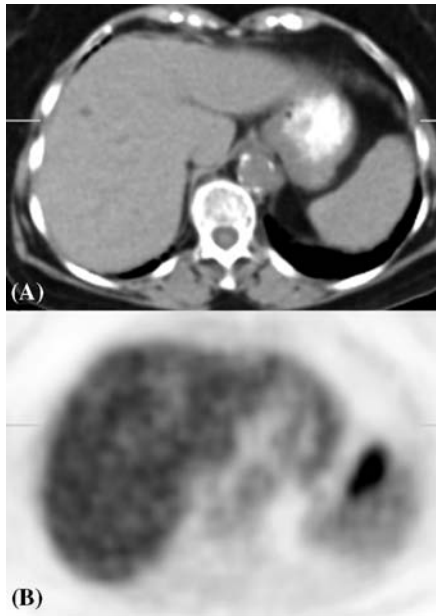


Figure 14 Splenic implant, ovarian carcinoma. PET/CT performed in a patient with recurrent ovarian carcinoma shows a relatively bland appearing spleen on the CT portion (A) performed in this case without IV contrast but clearcut metabolic activity corresponding to the medial splenic surface on the matching PET slice (B). *Abbreviation:* PET, positron emission tomography.

plaque-like thickening of the diaphragm. Involvement of the liver and spleen results in scalloping of the surface of these organs by low-attenuation masses (Fig. 14). The falciform, gastrohepatic, and gastrosplenic ligaments may be thickened and demonstrate soft tissue stranding. Tumors may be located in the porta hepatis, gallbladder fossa, lesser sac, and the surface of the stomach. Soft tissue masses on the bowel and mesentery cause a tethered configuration and may lead to bowel obstruction. In the pelvis, implants can involve the superior surface of the sigmoid, sigmoid mesocolon, uterosacral ligaments, lateral aspect of the rectum, the pelvic sidewall, bladder, cul-de-sac in front of the rectum and inguinal canals (126). Ascites fluid is helpful in the detection of small tumor implants. The presence of ascites is nonspecific, but usually indicates the presence of peritoneal metastases in the patient with ovarian cancer (8).

There are three pathways of lymphatic drainage by which ovarian cancer may spread. The principal lymphatic drainage of the ovaries parallels the gonadal veins in the infundibulopelvic ligament, terminating in the para-aortic and pericaval lymph nodes at the level of the renal arteries. Additional pathways of nodal spread are via the broad ligament to the pelvic sidewall nodes (internal iliac and obturator chains) and via the round ligament to the external iliac and inguinal nodes (Fig. 12). Sensitivity for

identifying intraperitoneal and lymph node disease in both primary and recurrent ovarian cancer likely depends on criteria for identifying PET/CT positivity. With a very high degree of suspicion, any activity on PET corresponding to small lymph nodes on CT might warrant a positive diagnosis. Possibly more specific, but less sensitive would be ascribing positivity to foci of increased activity (over background) corresponding to small nodes. In primary disease, enlarged nodes on CT, even if they are not metabolically active, have to be considered suspicious. For the most part, criteria for PET/CT are not described clearly in the literature. A short-axis diameter of greater than 1 cm is often used as the CT criterion for malignant nodes, with a reported accuracy of 88% in ovarian cancer (127). Hematogenous spread of ovarian cancer occurs later in the course of disease, with metastases most common to the liver, lung, adrenal gland, pancreas, spleen, bone and bone marrow, kidney, skin, and brain (8).

CT has been the primary imaging modality utilized in the staging of ovarian cancer. In early studies utilizing older CT equipment, the reported accuracy of CT in staging ovarian cancer ranged from 70% to 90% (127–130). While lymph nodes, even small ones, are generally easy to identify for peritoneal disease, confounding small bowel on CT, or bowel activity on PET may decrease the observer's accuracy. Small extra bowel deposits may be missed more easily. In all of these cases oral and IV contrast will help. In patients such as these studied with separate PET and CT, the size of peritoneal disease often limits sensitivity (131). The greatest limitation of CT is in detecting bowel surface, mesenteric or peritoneal implants less than 5 mm in size. Recently, the use of spiral CT demonstrated an overall sensitivity of 85% to 93% for detection of metastases with sensitivity of 25% to 50% for lesions measuring 1 cm or less (125). MDCT technology is also now widely available. The ability to obtain thin sections over a large volume with generation of higher resolution reformatted images in multiple planes will likely allow for increased detection of small implants, particularly in the detection of peritoneal carcinomatosis (7,59,132). Pannu and colleagues found improved sensitivity, specificity, and accuracy in the detection of peritoneal metastases when both axial and multiplanar images were reviewed (132). MRI may also be utilized for ovarian cancer staging (133). In a study of US, CT, and MRI staging of advanced ovarian cancer performed by the Radiological Diagnostic Oncology group in 118 patients with advanced ovarian cancer, CT, and MRI were found to be equally accurate, and either modality can be used to stage disease (134). Currently, no imaging modality allows microscopic spread of the disease to be ruled out, and full staging laparotomy is still required (124). As described above, failure to achieve optimal surgical cytoreduction usually results from large tumor deposits in critical nonresectable sites, and these patients may be

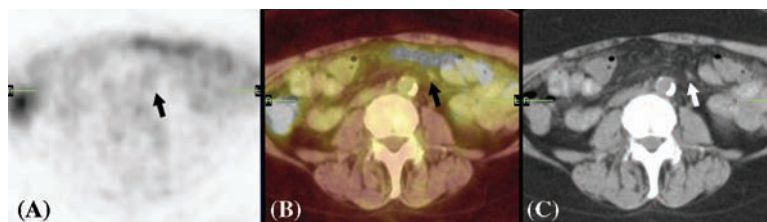


Figure 15 Omental caking. Relatively unremarkable image from the FDG PET portion of the study (A) in this patient with newly diagnosed serous carcinoma of the ovary when fused (B) to the CT slice (C) reveals mildly increased uptake corresponding to nodular soft tissue infiltration of the greater omentum (arrow). *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography.

better managed by neoadjuvant chemotherapy with interval or delayed cytoreduction. Both CT and MRI may be used to detect tumor implants greater than 2 cm at critical non-resectable sites such as subphrenic space, small bowel mesentery, porta hepatis, and lesser sac. In a study to determine the relative accuracy of CT and MRI in the detection of inoperable tumor sites prior to cytoreductive surgery in patients with primary epithelial ovarian cancer, Qayyum et al. (135) found that preoperative CT and MRI were equally accurate in the detection of inoperable tumor and the prediction of suboptimal debulking. The sensitivity, specificity, PPV, and NPV for the prediction of suboptimal debulking were 76%, 99%, 94%, and 96%. The overall accuracy of CT and MRI was 96% and 95%, respectively.

With PET alone, reliable sensitivity for disease is limited to lesions greater than 1 cm although clusters of carcinomatosis greater than 0.5 cm have been visualized on PET alone (Fig. 15) (131). This finding may explain the reports in the literature of relatively low sensitivity for even the combination of separately obtained CT and FDG PET for peritoneal carcinomatosis of 78%, compared with 57% for PET alone and 43% for CT alone although positive predictive values of either modality are high (131). Even with in-line PET/CT sensitivity for peritoneal lesions was only 50% for disease greater than 1 cm in size and 13% for lesions smaller than 1 cm (136). On the other hand, all lymph node metastases measuring 1 to 2 cm were identified. In another series using in-line PET/CT, detectability remained reliable down to 0.5 cm for peritoneal disease and for lymph nodes (137).

Using PET to Determine Prognosis

The search for value of FDG PET and PET/CT at the initial presentation of ovarian cancer has been more closely focused on the staging of ovarian cancer and prognostic information, once it has been diagnosed. Since FDG uptake appears to correlate with markers related to the aggressivity of ovarian cancer, FDG PET may add prognostic information (118) in patients initially diagnosed with ovarian carcinoma. While prognostic information may guide subsequent therapy, the more

important role may be in preoperative staging, identifying patients who can be debulked surgically and aiding in the optimal debulking which is the preliminary step to successful therapy (Fig. 16). In a small series of patients suspected to have ovarian cancer based on CA-125 levels, US and physical examination, CT alone was compared with FDG PET and CT combined (138). In the pelvis, the addition of PET to CT offered little improvement in sensitivity (72% vs. 76%), specificity (81% vs. 82%), accuracy (79% vs. 81%), PPV (48% vs. 50%), or NPV (92% vs. 94%). Outside the pelvis, however, PET plus CT had a 63% sensitivity versus the 24% for CT alone, a slightly better accuracy (85% vs. 93%) and a higher PPV (45% for CT alone vs. 88% for the combination). For overall staging, CT was accurate in 53% of the patients, but consensus readings of PET with CT staged 87% of the patients accurately. Both correct downstaging and upstaging occurred with the addition of PET.

In some patients where adequate surgical debulking is not possible, neoadjuvant therapy may play a role (139). In addition to staging, the use of FDG PET in assessing response to neoadjuvant therapy has been investigated (Fig. 16). In a series of 37 patients treated with neoadjuvant chemotherapy, a metabolic response was classified as a 20% decrease after the first cycle of therapy and a 55% decrease in SUV (the lesion showing the smallest change) after the third cycle of chemotherapy (140). Most of the metabolic response was seen within two weeks of initiation of chemotherapy. While these changes mirrored changes in serum CA-125, they did not correlate with histopathologic response at surgery. More importantly, however, a metabolic response at both the first and third cycle of chemotherapy showed a better correlation with survival than clinical response or histopathologic response assessed at surgery. FDG PET response predicted the ability to achieve optimal surgical debulking in 83% (15 out of 18 patients).

Recurrence

Patients treated for ovarian carcinoma are generally followed with a combination of pelvic exams, CT scans, and

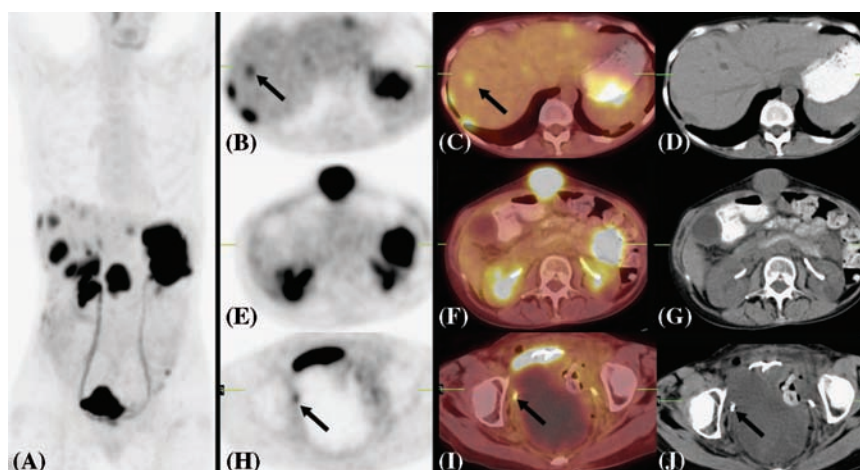


Figure 16 Stage IV ovarian cancer. Anterior image from the MIP of the PET portion of the PET/CT (A) performed in this 55 year old woman with newly diagnosed ovarian carcinoma shows extensive splenic and hepatic implants, omental disease, a tumor implant in the anterior abdominal wall (Sister Mary Joseph's nodule), and pelvic disease causing renal obstruction that required ureteral stenting. Transaxial PET (B), fused (C), and CT (D) slices through the upper abdomen show the metabolically active hepatic and peritoneal implants as well as a liver metastasis (arrow). Slightly more inferiorly, the PET (E), fused (F), and CT (G) images show the large left upper quadrant peritoneal implant and the large anterior, midline tumor implant. In the pelvis the photopenia of inactive ascites, and physiologic bladder and ureteral (stent) (arrows) activity is seen on PET (H), fused (I) and CT (J) slices. *Abbreviations:* MIP, maximum intensity projection; PET, positron emission tomography.

serum CA-125 determination. Routine second look surgery is controversial and no longer the standard approach (141). Second look laparotomy refers to systematic reexploration of the peritoneal cavity and retroperitoneum in asymptomatic patients who have completed a course of chemotherapy. The only patients who benefit from reexploration are those with microscopic or minimal disease. Patients with recurrent tumor greater than 2 cm are not surgical candidates (142) as they will not benefit from reoperation. Previous studies comparing conventional CT with second-look laparotomy found that CT could not replace second look surgery (143). A study to evaluate MRI identification of significant recurrent disease reported an accuracy of 83.3% (144). In an additional report using recurrent tumor greater than 2 cm as inoperable, MRI was 82% accurate in identifying patients who would not benefit from second-look surgery but this decreased to 38% for lesions smaller than 2 cm (127). Data on MDCT assessment of patients after primary cytoreductive surgery in evaluating for inoperability is not yet available.

The use of FDG PET, and more recently in-line PET/CT, has been explored more thoroughly in the setting of recurrent ovarian carcinoma (Fig. 17). While serum CA-125 is likely the most common tool employed to detect recurrence, PET has shown a slightly higher sensitivity in one series (145) and significantly higher specificity (100% for FDG PET compared with 33% for CA-125). Sensitivity and specificity of 83% for FDG PET alone have been reported, and in another series sensitivity was 84.6%

(145). However, that sensitivity fell in patients with low suspicion of recurrence to 65% and rose to 96% when CA-125 was elevated (146). While other authors have confirmed the sensitivity of FDG PET in recurrent ovarian cancer (145,147), Cho et al. (148) found only 45% sensitivity for detection with PET alone in patients with small volumes of disease. Low sensitivity in small volume disease and cystic lesions has been noted by others (145,149). The addition of CT to FDG PET has resulted in improvements in sensitivity and specificity in the study by Nakamoto et al. (147); sensitivity rose from 72.7% to 92.3% and specificity from 75% to 100%. Even in the case of a small volume disease, sensitivity increased from 45% to 58.2% with the addition of CT and the high specificity of PET alone of 99.7% was not compromised (148). However, in that series, the addition of PET to CT did not enhance the sensitivity of CT alone.

For in-line PET/CT, sensitivity for recurrent disease has also varied from 62% (150) to 72.7% (136) to 78% (151) and as high as 88.2% (152). In one series in the setting of elevated serum CA-125, per patient sensitivity was 83.3% for disease greater than 1 cm (153). Nonetheless, PET/CT increases the detection rate over PET or CT alone (Fig. 18) (152,154). While the PPV of PET/CT for recurrence is high, the NPV is hampered by the low sensitivity for lesions less than 0.5 to 0.7 cm (151,153).

Sensitivity for lymph node disease is higher than for peritoneal disease. Some authors suggest that in-line PET/CT will improve the detection of peritoneal disease compared to PET or CT alone (152,155). The addition

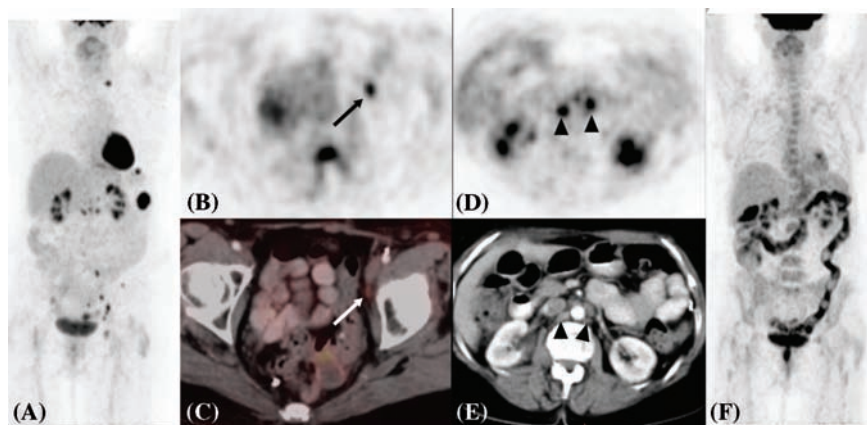


Figure 17 Recurrent ovarian cancer pre and posttherapy. Anterior view from an FDG PET MIP (A) in this patient with newly recurrent ovarian cancer shows lymphadenopathy in the pelvis, retroperitoneum, and left supraclavicular region as well as left upper quadrant implants. Transaxial slices from the FDG PET (B) and fused (C) from this pretreatment PET/CT shows the small but active left pelvic sidewall lymph node (arrow) and bowel implant. Higher up, the active retroperitoneal lymph nodes (arrowheads) are seen on PET (D) and CT images (E). After chemotherapy, the anterior MIP (F) from the repeat PET portion of the PET CT suggests that there has been a substantial metabolic response to therapy. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography; MIP, maximum intensity projection.

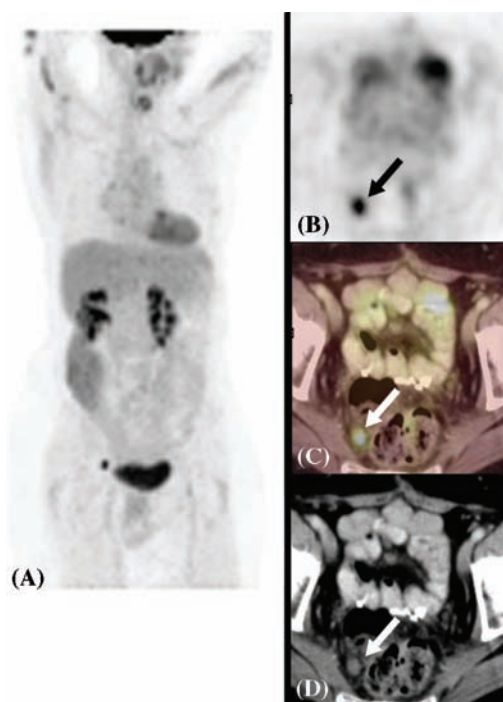


Figure 18 Peritoneal recurrence. Patient with history of complete response to debulking and chemotherapy for ovarian carcinoma three years earlier. The patient's CA-125 was rising. Anterior MIP from the FDG PET/CT (A) shows a focus in the right pelvis. On examination of transaxial slices a focus on the PET (B) is seen to fuse (C) to a soft-tissue nodule (arrows) at the right peritoneal reflection on CT (D). The nodule had been present on a diagnostic CT scan performed two months earlier but had grown over the interval. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography; MIP, maximum intensity projection.

of CT to PET helps in the detection of pulmonary metastases, for which PET alone is relatively insensitive (154,155). In certain areas, particularly the peridiaphragmatic abdomen, bladder regions remain problematic because of respiratory motion artifact and urinary activity, respectively (152). Some authors suggest that in the setting of a negative FDG PET image, the CT that shows a small amount of ascites should be regarded as suspicious since PET and CT may otherwise miss miliary spread (23). Furthermore, optimization of the CT technique, including use of IV contrast and adequate administration of oral contrast, may eliminate the cases where dedicated CT has identified disease even with a negative PET/CT.

In an early series of patients who had undergone optimal debulking and had normal CA-125, PET failed to predict microscopic residual/recurrent disease (149). Nonetheless, PET/CT plays an important role when CA-125 begins to climb in patients who have undergone curative intent debulking and chemotherapy (Fig. 18). While reports to date have concentrated on patients (136) with negative CT where PET alone has had a positive impact (156,157), with its increased availability, in-line PET/CT may become the examination of choice for these patients. PET has identified disease in 87.5% of one series of patients with asymptomatic rises in CA-125. The combination of CA-125 and PET had a 97.8% sensitivity in identifying recurrences (158), and in suspected recurrence, positive PET/CT may avoid second-look surgery if disease above the diaphragm is detected. Furthermore, in patients where second-look laparotomy is contemplated after curative intent treatment for initial presentation, PET/CT may offer an alternative (23). In one series of patients, 30 undergoing second-look

laparotomy for posttreatment evaluation and 25 undergoing FDG PET, the disease-free interval after negative examinations was not statistically significantly different (40.5 months after negative PET and 48.6 months after negative second-look laparotomy) nor was there a difference in the progression-free survival between the PET positive and laparotomy positive groups. PET/CT had a PPV of 93.8% and an accuracy of 81.8% for identifying disease greater than 1 cm permitting optimal cytoreduction to no gross disease in 72.2% of that series of patients with recurrences. Although it should be noted that second-line cytoreductive surgery is controversial (159), detection of metastases especially in the pelvis and abdomen can lead to successful secondary cytoreduction in those instances where it seems indicated followed by institution of second-line chemotherapy (153). The detection of the disease or unresectable disease may lead to the institution of chemotherapy alone. PET/CT only had a 50% NPV in that group of patients, but given the outcome data for PET alone, one might consider further surveillance rather than laparotomy. In a cost analysis assuming a 30% incidence of disease, PET alone had a 5% false-negative rate and led to a significant reduction in laparotomy from 70% to 5% of patients, with 35% patients undergoing the less invasive laparoscopy (160). While the application of this technology has been primarily investigated in the setting of initial recurrence, in practice, PET/CT may be useful in monitoring the response to second line chemotherapy (Fig. 17), initiating a change to third-line chemotherapy when patients demonstrate resistance.

ENDOMETRIAL CARCINOMA

About 10% of women who present with postmenopausal bleeding have endometrial carcinoma. In general, probably because of its tendency to present at an early stage, endometrial cancer has a good prognosis (161). Transvaginal US remains the most accurate and cost-effective imaging tool for the detection of primary endometrial cancer. Thickening of the endometrium or a focal mass in the endometrium are the most common findings on US, although imaging findings will vary depending on the size of the tumor and the stage of the disease.

Endometrial sampling for establishing a pathologic diagnosis (162) should follow. Although most patients with endometrial carcinoma then undergo surgery for staging and primary therapy, pretreatment imaging can help guide therapy as patients with extensive disease may no longer be appropriate surgical candidates or may require more extensive surgery with lymph node sampling and referral to a gynecologic oncologist (163). Preoperative clinical examination understages 22% of cases (164) increasing the importance of preoperative

imaging. Transvaginal sonography has limited accuracy in determining depth of myometrial extension, with reported accuracy of 68% to 99% (165–167). CT has been widely used as a staging modality for endometrial carcinoma to assess lymph node status and depth of myometrial invasion (Fig. 19).

Contrast-enhanced CT demonstrates endometrial carcinoma as a hypodense mass in a dilated endometrial cavity or in the uterine wall. The endometrial cavity may be fluid-filled due to tumor obstruction of the endocervical canal (168,169). Endometrial or myometrial tumor is usually intermediate in density between the less dense endometrial fluid and normally enhancing myometrium. When focal invasion of the myometrium is detected on CT, this finding usually corresponds to invasion of greater than one-third to one-half of the myometrium (169,170). CT staging criteria are based on the FIGO staging classification. Endometrial cancer involvement of the cervix (stage IIB) appears on CT as cervical enlargement greater than 3.5 cm in diameter and a heterogeneous hypodense mass in the cervical stroma (170,171). Stage IIIA is characterized by parametrial and pelvic sidewall extension or metastatic disease to the ovary (61). At CT, an obstructed uterus will appear enlarged with a distended fluid-density endometrial cavity surrounded by a myometrial wall of variable thickness (168).

Limitations of CT include differentiating a submucosal leiomyoma from uterine cancer, determining the depth of myometrial and cervical invasion and detecting rectosigmoid invasion. However, as in the case of cervical cancer, data describing the staging accuracy of CT in endometrial cancer are mostly derived from studies which predated recent developments of CT technology including helical and MDCT. In one published study assessing the use of helical CT for staging of endometrial carcinoma, the sensitivity and specificity of helical CT to detect deep myometrial invasion was 83% and 42%, respectively, and the sensitivity and specificity to detect cervical invasion was 25% and 70% (172). Further studies evaluating the accuracy of MDCT, including multiplanar reformatted images, are needed.

At MRI, the appearance of endometrial carcinoma is variable. Tumors are generally hyperintense relative to the myometrium on T2-weighted images and isointense on T1-weighted images (Fig 19) (163). Appearance of the tumor will depend on the size. Smaller masses may appear as an area of focal or irregular thickening of the endometrium, whereas larger tumors appear as polypoid masses that expand the endometrial cavity. There is variable enhancement of tumors with gadolinium. MRI usually demonstrates the junctional zone well and has shown good sensitivity for myometrial invasion and cervical invasion. Myometrial invasion is best evaluated on T2-weighted images or postcontrast images. An intact junctional zone indicates lack of myometrial invasion. Myometrial invasion

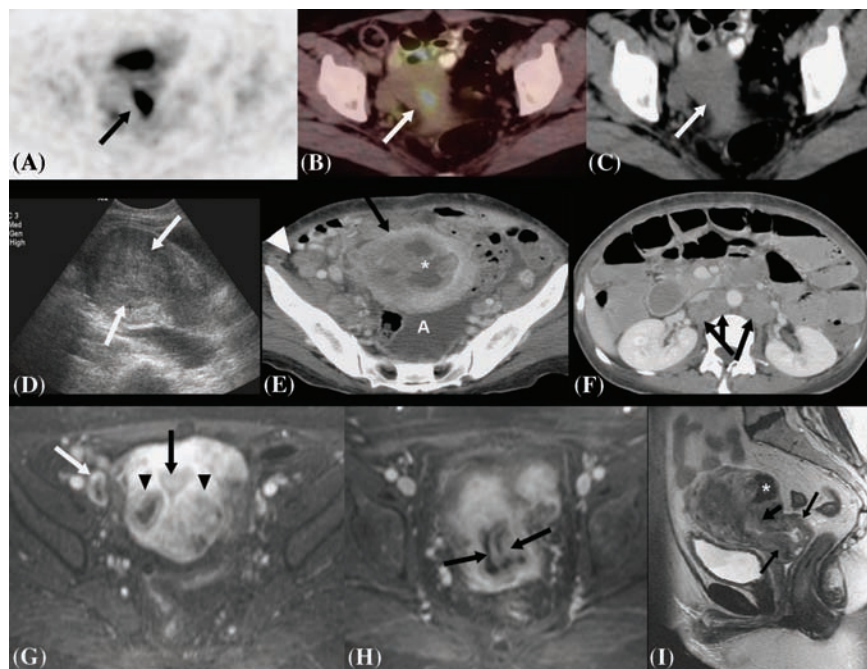


Figure 19 Primary endometrial carcinoma. PET/CT (A–C) performed in this 65-year-old woman with a history of lung cancer shows intense uptake in the endometrial cavity (*arrow*). Biopsy showed adenocarcinoma of the uterus. (D) Sagittal transabdominal US of the pelvis in a different patient demonstrates markedly thickened endometrium containing tumor (*arrows*). (E) Contrast-enhanced CT in this patient demonstrates the markedly distended, endometrial cavity filled with heterogeneously enhancing tumor (*asterisk*). There is invasion of the myometrium, which is markedly thinned. The arrow indicates extension of tumor through the serosal surface of the uterus on the right. The arrowhead indicates enlarged right external iliac nodal chain. (F) CT of the upper abdomen demonstrates enlarged retroperitoneal lymph nodes (*arrows*). (G) MRI in a different patient. Axial T1-weighted GRE image with gadolinium demonstrates enhancing tumor within the endometrial canal (*black arrow*). Intramural fibroids are also present (*arrowheads*). An enlarged, heterogeneous enhancing right pelvic sidewall lymph node is also demonstrated (*white arrow*). (H) More inferior image demonstrates extension of endometrial tumor into the cervix (*arrows*) which is enlarged and heterogeneously enhancing. (I) Sagittal T2-weighted FSE image demonstrates tumor within the lower endometrial canal (*thicker arrow*) as well as cervical extension (*thinner arrows*). Low-signal intensity intramural fibroid again noted (*white asterisk*). Abbreviations: PET, positron emission tomography; US, ultrasound; FSE, fast spin-echo; A, ascites.

of greater than 50% indicates stage 1C disease. Contrast-enhanced MRI offers a high accuracy in assessing parametrial involvement. MRI has been shown to achieve a sensitivity of 87% for myometrial invasion and 80% for cervical invasion with a specificity of 91% and 96%, respectively (173) but may overestimate the primary tumor volume. In one meta-analysis, the inclusion of contrast-enhanced MR images significantly affected the posttest probability of deep myometrial invasion in patients with all stages of endometrial carcinoma (174). MRI is currently considered the most accurate modality for pretreatment evaluation of endometrial cancer with advantages including superior contrast resolution and multiplanar imaging capability. The reported overall staging accuracy of MRI ranges from 83% to 92% (55,164,175–178). A meta-analysis to compare staging accuracy of US, CT, and MRI demonstrated that MRI with gadolinium was significantly better than CT or US in demonstrating myometrial invasion (179).

Identification of primary endometrial carcinomas on FDG PET/CT is more often incidental or occurs in the context of looking for extrauterine disease in women already diagnosed (Fig. 19). Identification in primary tumors was possible in 84% of patients in one series (180). In the remaining patients, uptake was equivocal, possibly on the basis of the small size of the tumors.

Staging

Once the diagnosis is established, identification of extrauterine disease may significantly change treatment and prognosis. Elevated CA-125 tends to be associated with an increased incidence of extrauterine disease in patients with primary endometrial cancer at initial presentation (181). Also, aggressive cell type, suspicious physical

examination, positive endocervical curettage portend extrauterine involvement (182). Between 10 and 30% of women have lymph node metastases even with early clinical stages (183,184). In the past, extrauterine staging has been accomplished by lymph node sampling at the time of definitive surgery focusing on the pelvis with a variable degree of retroperitoneal sampling.

CT and MRI in Staging Extrauterine Disease

CT has the greatest impact in clinical stage III tumors by confirming parametrial and sidewall extension, detecting pelvic lymphadenopathy or upstaging tumors to stage IVB by detecting extrapelvic metastases. The role of CT in evaluation of endometrial carcinoma includes accurate staging of patients who have an equivocal pelvic examination or medical contraindication to surgical staging, screening for lymphatic or peritoneal metastases in patients with a poorly differentiated carcinoma or sarcoma, and to confirm advanced stage III–IVB cancers (34). The reported accuracy of conventional CT in staging endometrial carcinoma ranges from 84% to 88% (29,171). Compared with accuracy in identifying intrauterine disease and local spread, CT has higher accuracy in identifying lymphadenopathy, omental disease and liver metastases. As in the case of cervical cancer, lymph nodes greater than 1 cm are highly suspicious for metastatic lymphadenopathy (Fig. 19). MRI and/or CT have been only moderately helpful in delineating extra uterine nodal spread. In one series of 56 women studied preoperatively with CT, sensitivity was 57% and specificity 92% for nodal involvement (185). MRI also has shown poor sensitivity (50%) but high specificity (>90%) (173). MRI is gaining acceptance as the initial imaging modality in patients with high risk of extrauterine disease, eliminating the need for multiple imaging modalities (186).

PET and PET/CT in Staging Extrauterine Disease

In a series of patients with relatively early-stage disease and only an 11% incidence of lymph node metastases, PET showed only 60% sensitivity and 98% specificity on a regional basis and 67% sensitivity and 94% specificity on a per patient basis. While a positive PET alone may be meaningful in patients with primary endometrial cancer, a negative PET clearly does not obviate lymph node sampling. In a study assessing the impact of combining separate CT or MRI with FDG PET, the addition of PET to MRI or CT significantly improved lesion detection and accuracy although specificity was not altered especially in the detection of pelvic soft tissue tumor and metastatic lymph nodes (181). In these later-staged patients, FDG PET alone led to treatment changes in

22%, either more extensive lymph node dissections, resection of distant metastases, the addition of adjuvant radiation therapy or, in one case, a change to palliative treatment. While MRI has gained acceptance as the initial imaging modality in patients with high risk of extrauterine disease over CT alone (186), the addition of FDG PET or PET/CT may enhance the sensitivity of both, especially by raising suspicion for disease in less than 1 cm nodes that do demonstrate mild to moderate activity and that might otherwise have been missed on CT.

Staging Distant Disease

While a touted advantage of PET/CT in staging has been the detection of distant metastases, in the series of early-stage patients by Horowitz et al. , all the PET (alone) foci detected were false positive for metastases or even other cancers (180). In later stage patients, FDG PET combined with MRI or CT significantly improved detection of extrapelvic disease over MRI or CT alone (181), although in one patient with primary disease, a suggestion of a bone metastasis was incorrect.

Surveillance and Recurrence

Endometrial cancers recur in only about 3% of early tumors and up to 13% over all. The majority of these recurrences occur within the first three years of curative intent treatment for the primary tumor and 30% may be symptomatic. While some authors have suggested that treatment of asymptomatic recurrences provides a survival benefit, this has not always been shown to be the case. Survival benefit may be seen in patients who recur at a relatively later time point after initial treatment (187). No recommended algorithm for the follow-up of patients has been validated. Usual follow-up after treatment of the primary tumor consists of physical examination, vaginal cytology, and chest radiographs. These tests have been the most commonly employed tools in surveillance for recurrence. CA-125 is employed inconsistently across practitioners and has had about a 55% sensitivity for recurrences (188). Morphologic imaging, CT, MRI, or US, tends to have low detection rates, but the yield increases with the risk conferred by the primary tumor (187). While local recurrences may carry a better prognosis, early detection of distant recurrences offers no survival benefit. Nonetheless, detection of distant recurrences may avoid the morbidity of curative-intent salvage therapy.

While the mainstay of therapy for recurrent endometrial cancer is systemic, usually chemotherapy [doxorubicin and cisplatin or paclitaxel and epirubicin (189)], or hormonal therapy, surgical debulking (190) and brachytherapy for vaginal recurrences (191,192) have been

reported. Clearly, identifying the location and extent of disease becomes important in selecting and testing the efficacy of these therapies. The most common sites of extrapelvic metastases are lung, abdomen, aortic and supraclavicular nodes, brain, liver, and bone.

CT Features

CT has generally served as the modality of choice for detection of recurrent or metastatic disease because of its ability to rapidly screen the pelvis, abdomen, and chest. CT also offers the ability to guide percutaneous biopsy. CT features of recurrent carcinoma include a central pelvic mass often arising from the vaginal cuff, pelvic and para-aortic lymph node metastases, mesenteric, peritoneal omental, and liver metastases (Fig. 20) (29,171). Recurrent uterine sarcoma may also include widespread hematogenous metastases to the spleen, kidneys, bowel, and abdominal wall.

PET Features

Local recurrence, either at the vaginal cuff or in the vaginal vault as with cervical carcinoma is identified by increased uptake in this location. Especially with the

vaginal cuff, recurrence is often accompanied by a change in the appearance of the CT soft tissue (Fig. 20). A vaginal vault uptake may be more difficult to differentiate from urinary contamination. As with cervical cancer, radiation changes may complicate the interpretation on PET (193).

Lymph nodes that show activity even when they do not meet size criteria for CT may harbor tumor (Fig. 20). Difficulty arises in distinguishing tiny nodes with mild to moderate activity from very close vascular activity.

In a group of patients treated initially with surgery, the sensitivity of FDG PET combined with CT or MRI (not in-line), gave improved sensitivity for detection of recurrence over CT/MRI alone (Fig. 20) and improved specificity over the use of tumor markers (194). The detection of a previously unknown disease changed management in a third of these patients. Others have confirmed this finding in a group of patients with suspected recurrence on the basis of elevated tumor markers, FDG PET contributed to MRI/CT increasing the area under the curve of the receiver operator curve significantly (181). FDG PET alone detected recurrence or disseminated disease in half the patients scanned for surveillance and accurately confirmed the absence of disease in about one fifth. More importantly, PET was useful in clinical management decisions, supporting the use of salvage treatment or the

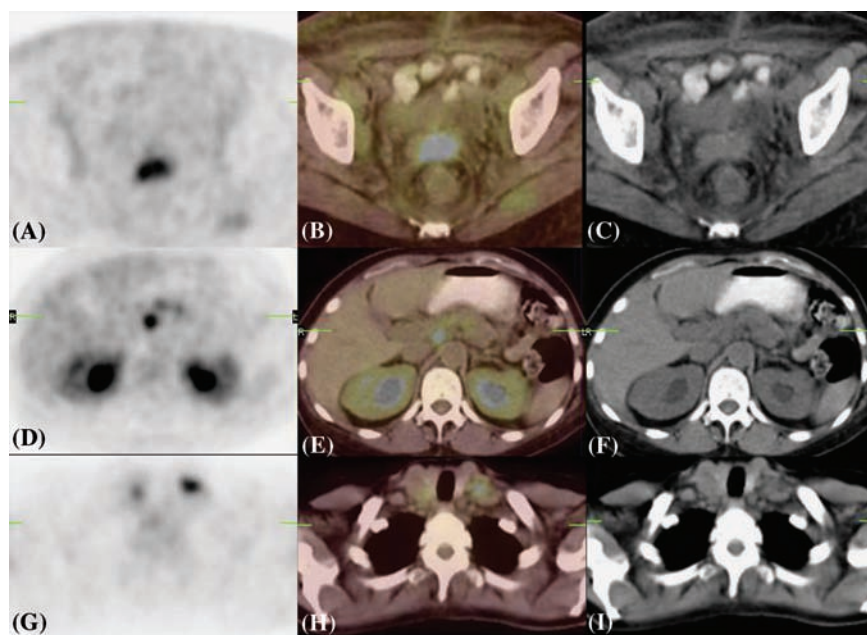


Figure 20 Endometrial cancer recurrence: FDG PET CT performed in a patient who had been treated with curative intent two years earlier. Her tumor markers had been rising. Transaxial PET (A), fused (B), and CT scan (C) show a metabolically active and slightly enlarged vaginal cuff consistent with recurrent disease. At the level of the kidneys, PET (D), fused (E), and CT (F) slices show metabolically active and borderline enlarged lymph nodes in the retroperitoneum. Finally, PET (G), fused (H) and CT (I) slices through the lower neck show left supraclavicular lymph node activity making systemic therapy an imperative. *Abbreviations:* FDG, fluorodeoxyglucose; PET, positron emission tomography.

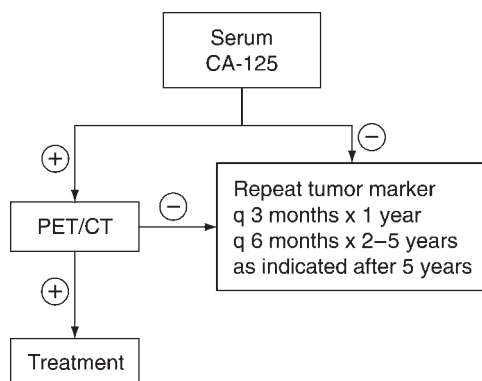


Figure 21 Algorithm for surveillance of endometrial carcinoma using PET/CT and serum CA-125. *Abbreviation:* PET, positron emission tomography. *Source:* From Ref. 195.

use of palliative therapy. After salvage therapy in a group of seven patients, the PET finding was true negative in spite of positive CT scans and true positive for disseminated disease. Belhocine et al. showed that FDG PET improved detection of recurrence in a greater number of patients than routine clinical or radiologic assessment (Fig. 21) (193). The sensitivity for recurrence was 96% in this series. The advantage of PET was seen in asymptomatic patients. Recurrences were both local and distant in half the cases and confined to abdominopelvic recurrence in a little more than a third. As with other reports, management was influenced by PET in 35% of the patients. The true sensitivity and specificity in the setting of surveillance and recurrent disease has not been established for in-line PET/CT.

In surveillance and monitoring of recurrent disease, PET/CT likely will have its greatest impact on patients who initially presented with later-stage disease, although PET-detected recurrence may occur in patients with early-stage disease as well. Some authors have suggested that CA-125 monitoring in conjunction with PET ought to be the first line in surveillance for recurrence and treatment response after recurrence (193).

SUMMARY

Physiologic activity in the adnexa and/or endometrium is a common finding in premenopausal women. Identification of this activity needs to be correlated with the patient's age and menstrual status. Application of PET/CT to the staging, monitoring, and restaging of cervical cancer is well accepted. FDG PET/CT will add information essential to proper management and treatment selection. In ovarian cancer, FDG PET/CT adds to staging of the primary, monitoring of recurrence, choice of treatment strategies in recurrent disease, and assessment of

treatment response. Although the application of FDG PET in the management of endometrial cancer is not as straightforward, there does appear to be some utility in evaluating patients who have rising tumor markers and are suspected of recurrence. Whether PET/CT will play a standard role in restaging at recurrence or assessing treatment response is not yet established.

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Using PET/CT in Evaluating Cancers of the Genitourinary Tract

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PROSTATE CANCER

Introduction

The American Cancer Society predicted an incidence of 218,890 new cases of prostate cancer in 2007. It is the most common cause of cancer in men, and second only to lung cancer in the number of yearly deaths (27,050). Early prostate cancer is usually asymptomatic, whereas more advanced disease typically presents with urinary symptoms. Prostate-specific-antigen screening is easy to perform, sensitive, and in widespread use, but limited in terms of specificity (1).

The prostate gland is divided into a peripheral, transitional, and central zone. Most prostate cancers occur in the peripheral zone, and the vast majority of these are adenocarcinomas. The Gleason grading system has been developed to score the histological aggressiveness and aid in prognosis and therapy planning (2).

Digital rectal exam and conventional transrectal ultrasound have not been sufficiently accurate to allow directed biopsy of the prostate in patients with suspected cancer. For this reason, tissue sampling of multiple regions based on subdividing the gland into multiple zones has been developed. Refinement of an imaging

modality that would allow a more focused approach would represent a significant advance in the diagnosis of prostate cancer by improving yield per biopsy session and reducing the number of required repeat biopsies (2). Once the tumor is diagnosed, proper staging is required in order to select the appropriate treatment plan, which includes myriad options including watchful waiting, radiation therapy, chemotherapy, and surgery. Metastatic disease commonly involves the lymph nodes of the pelvis and retroperitoneum, with advanced disease typically involving the bones, lungs, and liver (3).

Conventional Imaging

Ultrasound

Ultrasound is typically used to orient the biopsy needle when sampling the various regions of the prostate in suspected prostate cancer. It is also useful after diagnosis for placement of brachytherapy seeds (4). Most tumors are hypoechoic or isoechoic although some are hyperechoic. Unfortunately, hypoechoic lesions are nonspecific and can be seen in prostatitis, atrophy, and other benign conditions. For this reason, the utility of ultrasound in the precise localization of prostate cancer is limited (2).

MRI

Magnetic resonance imaging (MRI) has become an area of great interest and innovation in the imaging of the prostate. It is currently of use in intermediate risk patients to examine the extent of the primary tumor. MRI is useful to look for evidence of capsular penetration, neurovascular, seminal vesicle, or adjacent organ invasion. It is also very sensitive and accurate for the detection of skeletal metastases, and recently whole-body MRI scanners with radio-frequency coils capable of parallel imaging have enabled whole-body imaging in a reasonable scan time. Although it is feasible to use MRI for whole-body scanning, which, based on preliminary data, shows great promise for detecting bone metastases, whole-body MRI scanners are not universally available and further investigation is warranted in larger patient populations. At this point, bone scintigraphy remains the screening test of choice. MRI combined with injection of ferromagnetic particles is also of emerging interest for the detection of lymph node metastases, but this type of contrast agent is not yet FDA approved for use in the United States as of this date. New MR spectroscopic techniques aimed at identifying increased levels of choline in the prostate are expected to improve overall staging of prostate cancer but currently require extensive expertise for proper interpretation (2).

Computed tomography

Computed tomography (CT) is not useful in the staging of localized primary prostate cancer but is useful for the detection and follow-up of metastatic disease. In advanced disease in the prostate, CT will be positive (Fig. 1). It is generally recommended in patients with PSA levels greater than 20 ng/mL who are considered to have an increased risk for nodal disease (5). Overall the sensitivity of CT for the detection of lymph node metastases is limited and has been reported to range from 25% to 85% (6). Sensitivity of CT is likely to remain low given



Figure 1 Locally recurrent prostate cancer on CT in a 75-year-old male. CT demonstrates a partially enhancing, heterogeneous mass at the prostatectomy bed (arrowhead).

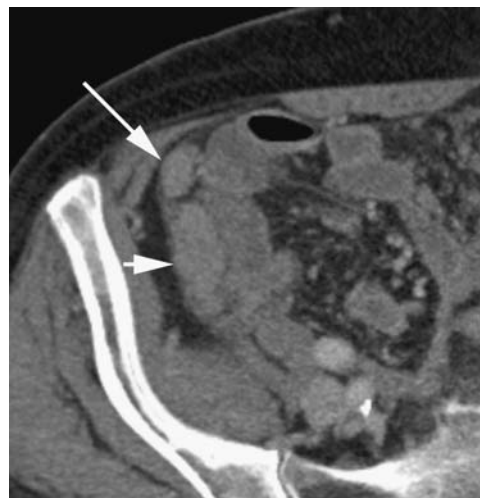


Figure 2 Peritoneal metastases of prostate cancer. Two-slice maximum intensity projection demonstrates peritoneal nodularity (arrows) in the right pelvis. Note the more homogeneous, solid density compared with adjacent bowel, which demonstrates central decreased density because of luminal contents.

the more frequent diagnosis at earlier stages of the disease resulting from modern screening techniques. In patients with very advanced primary tumors, CT may prove more useful for the detection of occult distant disease that may affect management (Fig. 2).

Lymph node metastases typically present as enlarging nodes greater than 1 cm although small lesions can frequently escape detection and appear as morphologically normal lymph nodes. One of the most common CT findings in metastatic prostate cancer is the presence of sclerotic osseous metastases. Lesions are often multiple and tend to involve the axial skeleton. CT can be useful to monitor the progression of the disease but caution must be taken in the setting of increasing sclerosis as this can be due to treatment response and not due to the growth of tumor. Pulmonary metastases are often small, round, solid, peripheral, and multiple in appearance. Equivocal findings in the lung require either follow-up or biopsy for definitive characterization.

PET and Prostate Cancer

Initial diagnosis

Fluorodeoxyglucose positron emission tomography (FDG PET) is limited in the initial diagnosis of prostate cancer because of low FDG uptake within prostate tumor cells, and high levels of excreted FDG in the urine which interferes with image interpretation. In 1996, Effert studied FDG uptake in primary prostate cancer (Fig. 3) and noted low FDG uptake in 81% of primary tumors (7). In a similar study of biopsy-proven primary prostate cancer,

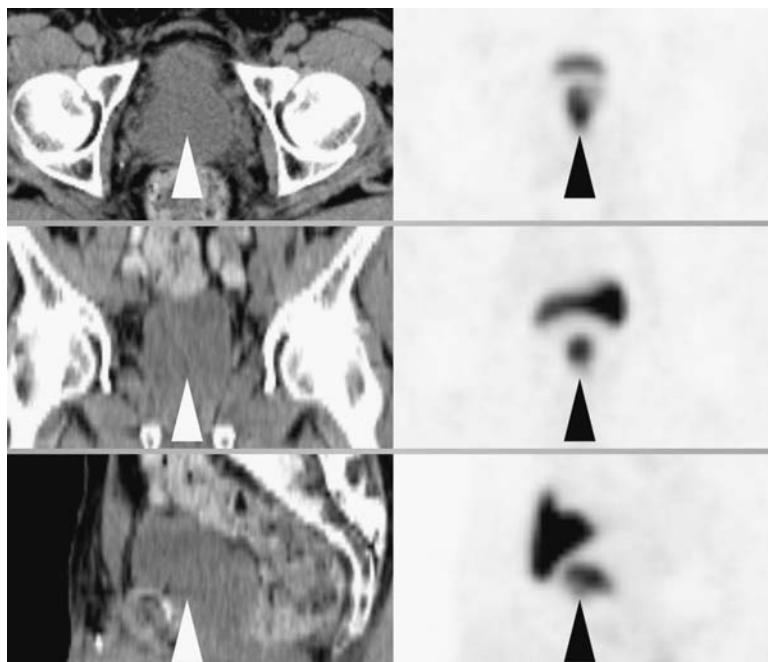


Figure 3 Primary prostate cancer. A 69-year-old male with lung cancer and newly diagnosed prostate cancer. PET/CT demonstrates intense FDG uptake in the prostate at the location of the primary tumor.

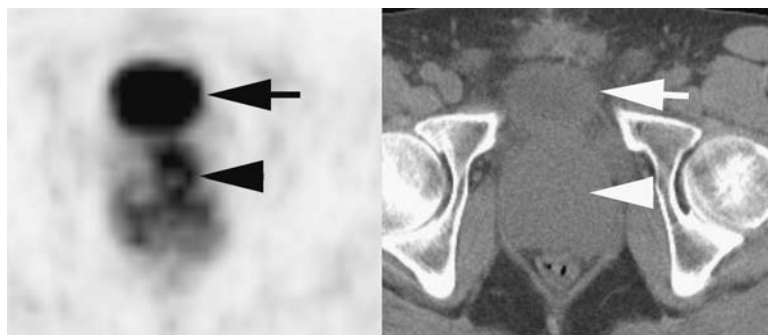


Figure 4 Primary prostate cancer. Intense heterogeneous uptake throughout the prostate (*arrowhead*) due to a large primary tumor. Note bladder activity anteriorly (*arrowhead*). This appearance is not typical for urine in the prostatic urethra, which is usually focal and midline. Diffuse intense uptake has been reported in prostatitis.

the FDG PET result was negative in 23 of 24 organ-confined prostate cancers and only mildly positive in one tumor (Fig. 4) (8).

Other tracers have shown greater promise in the detection of primary prostate cancer. In 2007, Scher and coworkers reported on the accuracy of ^{11}C -choline PET and PET/CT in the detection of primary prostate cancer. In 58 patients with suspected primary tumor, 37 were proven to have the disease and ^{11}C -choline PET and PET/CT demonstrated a sensitivity of 87% and a specificity of 62% for the detection of the primary tumor (9). Additional work by Reske and coworkers using ^{11}C -choline PET/CT suggests that this tracer may be useful for diagnosis and precise localization of the primary tumor, particularly

facilitating the evaluation of patients who require repeat biopsy (10). Further work is needed to determine if their results can be reproduced and implemented in routine clinical practice. Additional authors have reported success with ^{11}C -choline for defining the primary tumors (11,12), and increased availability of this tracer or a fluorinated version of it may prove useful to a broader range of patients in future. Delayed or dual-phase imaging with ^{18}F -fluorocholine may be of particular interest in improving localization of tumor (13).

Initial staging

The use of FDG for the detection of metastatic prostate cancer has also been disappointing. In 1996, Shreve found

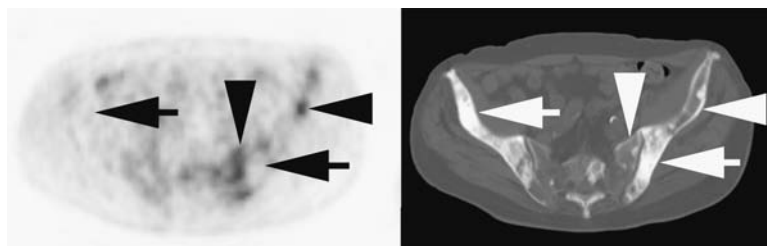


Figure 5 Complementary information provided by PET and CT in prostate cancer. PET demonstrates areas of viable tumor (arrowheads) that are not visible on CT, whereas CT demonstrates sclerotic metastases that are largely inactive (arrows).

a sensitivity of 65% for the detection of osseous metastases, which was inferior to bone scintigraphy (14). This finding was confirmed in a study by Yeh that noted the uptake of FDG in only 18% of bone metastases (Fig. 5) (15). Sanz reported similar findings in 1999, with FDG PET unable to reliably detect lymph node metastases (16). FDG has been estimated to detect nodal metastases with a sensitivity ranging from 0 to 50% and a specificity ranging from 72 to 90% (17).

Tracers other than FDG have also shown promise in the detection of metastases. Scher recently reported an 82% per-patient sensitivity for the detection of prostate cancer metastases using PET and PET/CT with ^{11}C -choline (9). ^{11}C -acetate has been proposed by some to be more sensitive for the detection of local nodal metastases and has had mixed results when compared with FDG for the detection of bone metastases (18–20). ^{18}F -fluorocholine has been investigated for the detection of metastases with conflicting results (21–24) and thus requires further study.

Recurrence detection

FDG has been only marginally useful in the evaluation of patients with suspected recurrent prostate cancer (Fig. 6), mainly because of the low FDG uptake within most small metastases. Seltzer reported equal performance of FDG PET and CT for the detection of suspected recurrent

disease with only 50% sensitivity in patients with PSA elevations greater than 4 ng/mL (25). Others found that FDG PET only detected disease in 31% of patients with PSA relapse (26). In 1999, Hofer and coworkers examined the ability of FDG PET to detect local recurrence after prostatectomy and found low FDG uptake with no difference between prostate hyperplasia, prostate carcinoma, postoperative scar, or local recurrence (27). Overall, it appears that the use of FDG for recurrence detection is limited.

Other tracers also appear more useful for recurrence detection. Several studies have suggested that ^{11}C -acetate detects more recurrent soft tissue disease than FDG (18,19). However, one study by Fricke and coworkers suggests that FDG may detect more bone metastases than ^{11}C -acetate (19). Others have found that ^{11}C -choline and ^{18}F -choline may be superior to FDG for the detection of recurrent disease (28,29). Overall the literature is mixed and further clarification is required before these tracers should be used clinically.

Treatment response

There is a limited literature examining the utility of FDG PET in prediction of treatment response to prostate cancer. In separate studies, Oyama and Morris have demonstrated a correlation between changes in FDG uptake and PSA

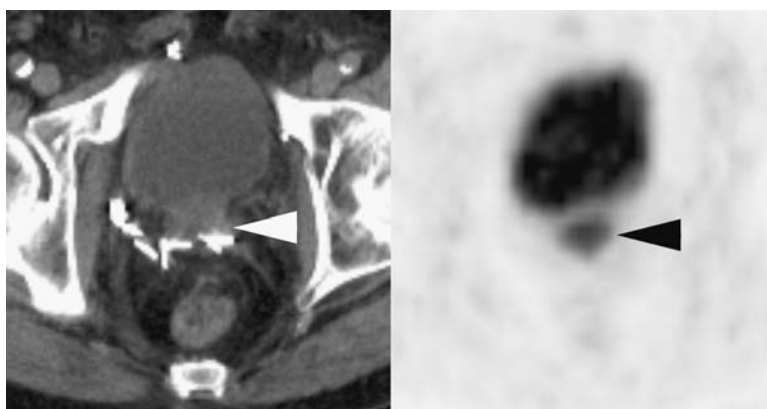


Figure 6 Locally recurrent prostate cancer. PET/CT demonstrates focal intense uptake fusing with a mass at the prostate bed (arrowheads). This lesion would have been difficult to correctly classify on CT alone.

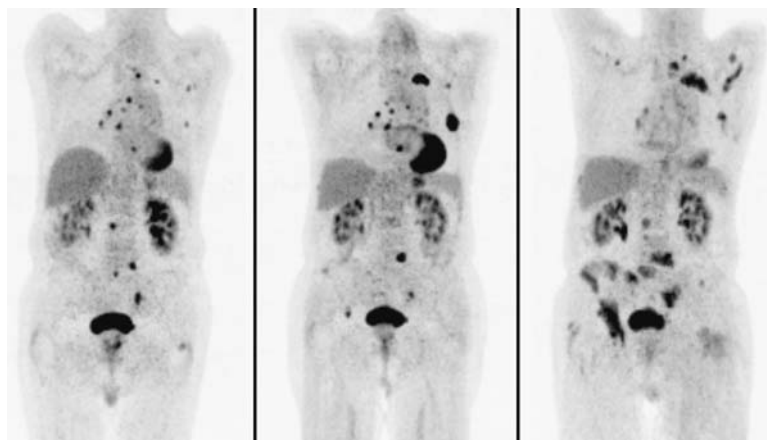


Figure 7 Treatment response monitoring in advanced prostate cancer. Baseline PET/CT (*left image*) compared with posttreatment study (*middle image*) demonstrates progression of disease in the chest and a mixed response below the diaphragm. Therapy was changed resulting in partial improvement of soft tissue metastases in the mediastinum and overall progression of bone metastases (*right image*). PET/CT allows for global assessment of therapy response in advanced prostate cancer.

response in patients undergoing treatment for metastatic disease (Fig. 7) (30,31). FDG, ^{11}C and ^{15}O PET may also be useful in monitoring anti-angiogenic therapy in prostate cancer (32). DeGrado and coworkers have also shown decreases in ^{18}F -choline uptake in metastases that are responding to anti-androgen therapy (33).

Other tracers

A closer look at tracers other than FDG are warranted even though they remain investigational. ^{11}C -acetate, a molecule that is used in cell membrane synthesis has been shown to concentrate in some malignant tumors. In a recent study, Albrecht demonstrated that this tracer could detect local recurrence in five of six patients (34). Sandblom and coworkers have also demonstrated the ability of ^{11}C -acetate to detect local recurrence rate with 75% sensitivity and a false-positive rate of 15% (35).

Another tracer of great interest is ^{18}F -fluoride, which when combined with PET/CT, demonstrates improved sensitivity and specificity compared with planar and single-photon emission computed tomography (SPECT) for the detection of osseous metastases (36). It remains to be seen if this tracer will gain cost effectiveness and widespread use. Imaging of prostate with ^{11}C -methionine (37) and the androgen receptor agent FDHT (38–40) are also under investigation and not yet ready for clinical use.

Added value of PET/CT

PET/CT potentially offers additional value in terms of better localizing tracer uptake within the prostate (Fig. 3 TURP). In addition, it could help to better characterization of lesions outside of the gland. Several studies have combined an analysis of new tracers with combined PET/CT scanners. No comparisons of PET/CT and PET

alone or PET combined with separately viewed diagnostic CT have been performed. Given the extensive literature already demonstrating the added value of PET/CT, it is likely that imaging of the prostate will improve with this modality compared with PET alone.

PET/CT has been used to correlate focal choline uptake with the precise location of biopsy samples taken in patients with prostate cancer (41). A high false-negative rate and limited sensitivity of choline-PET for the detection of primary tumors has been a limiting factor. However, a more recent study by Martorana suggests good sensitivity for localization of nodules measuring 5 mm or greater (11). Others have found that adding CT to ^{18}F -fluoride PET results in increased sensitivity and specificity compared with bone scan or PET alone (36). ^{18}F -choline PET/CT has potential value in radiation therapy planning (42). The growing implementation of PET/CT around the world for numerous types of malignancies suggests that it will probably become the standard even before controlled studies determine its advantage (or lack thereof) over PET alone.

Conclusions Regarding PET and PET/CT in Prostate Cancer

In summary, FDG PET has been shown to be of limited utility in the initial diagnosis, staging and restaging of prostate cancer. It probably plays its most valuable role in the monitoring of treatment response in select patients with aggressive, typically hormone-resistant disease. ^{11}C -choline and ^{11}C -acetate are promising new tracers for the detection of prostate cancer and, in particular, local metastases but are limited in terms of availability and short half-life. ^{11}C -choline may have a defined role in

detecting primary tumors that appear to be superior to FDG. ^{18}F -choline is of particular interest because of its longer half-life and may find more use as PET technology and familiarity with this tracer grows. ^{18}F -fluoride PET for bone imaging may be superior to bone scintigraphy but is not yet cost effective and has not been proven to significantly improve clinical management over bone scanning alone. ^{11}C -methionine and ^{18}F -fluoro-dihydrotestosterone are currently under investigation as new tracers for prostate cancer and data regarding their clinical use is limited.

RENAL CELL CARCINOMA

Introduction

The American Cancer Society predicted an incidence of 51,190 new cancers of the kidney and renal pelvis in 2007 with 12,890 deaths. The majority of these tumors are renal cell carcinomas (RCC). Diagnosis is often made by imaging after patients present with hematuria, a flank mass or flank pain. Ultrasound, CT, and MRI have been increasingly used to diagnose and stage renal cell carcinoma. A general overview of CT imaging of the kidney will be provided below followed by a discussion of how PET/CT contributes to the radiological armamentarium for RCC.

CT Imaging of the Kidney

CT Imaging Technique and Protocol Pearls

Renal masses are often found incidentally and may be indeterminate because of their small size and technical limitations. For optimal characterization of a renal mass on CT imaging, unenhanced, followed by enhanced, imaging is required. An adequate contrast bolus is required and the timing of imaging is critical as the corticomedullary phase imaging may obscure lesions. Slice thickness should be less, at least less than one-half the diameter of the mass. Density measures may be variable and less reliable with multidetector CT imaging because of a phenomenon called pseudoenhancement. Enhancement postcontrast is typically considered an elevation of greater than 10 HU. However, if multidetector computed tomography (MDCT) technique is employed a higher threshold of greater than 20 HU should likely be used for lesions smaller than 1.5 cm because of pseudoenhancement (43). Using another fluid filled structure for comparison may be helpful such as a known simple fluid density cyst, the gallbladder, or bladder. Drawing regions of interest to measure HU over these regions pre- and postcontrast can help for comparison to assess for relative enhancement. CT imaging parameters for pre- and post-contrast imaging should be kept constant across both

studies to ensure reliable comparison between enhanced and unenhanced images. HU measurements may be overestimated particularly when assessing small lesions surrounded completely by renal parenchyma in the setting of a dense nephrogram or as a result of streak artifact from a dense urogram. If a lesion remains indeterminate despite optimal CT technique, then close follow-up in six months or MRI may be useful. MRI is also warranted if the patient cannot receive iodinated contrast agents because of abnormal renal function, allergy or if radiation exposure need be limited. RCC tends to be slow growing and with small renal lesions smaller than 3 cm, the incidence of metastasis is low (<2%).

Normal Anatomy

Kidneys may be smooth or lobular in contour and may be divided in the upper, interpolar, and lower pole regions. The kidney is composed of an outer cortex and medullary pyramids the apices of which are called the papillae and project into the calyces. The calyces converge into the renal pelves and ureters. Kidneys range in size depending on adult patient size varying from 9 to 12 cm in length. There are many anatomic variants including duplication with an upper and lower pole moiety, each with separate collecting systems and ureters. This may be unilateral or bilateral. In patients with duplication, there can be obstruction of the upper pole collecting system. Kidneys may be ectopically located in the pelvis or there may be fusion of the right and left kidney in the midline referred to as a horseshoe kidney.

Renal Calcification

Renal calculi are easily detected on unenhanced CT imaging but may be obscured on enhanced CT images. Renal calculi can be described on unenhanced CT as hyperdense punctate, round, ovoid, or linear hyperattenuating structures that can be found in the kidney, collecting system, ureter, bladder, or urethra. It may be difficult to identify calculi if the contrast opacifies the collecting system unless window level settings are adjusted, and unless the stone is denser than the contrast or large in size. Obstruction secondary to renal calculi leads to renal enlargement, hydronephrosis, or hydroureteronephrosis depending on the level of the obstruction as well as perinephric stranding and fluid. On enhanced CT, a delayed nephrogram may be present indicating obstruction and resulting delay in contrast excretion.

These CT findings may also be seen in the setting of infection. Urinalysis and symptomatology are helpful for differentiating between infection and other disease processes. Contrast-enhanced CT imaging may also reveal other signs of infection such as bladder or ureteral or pelvocalyceal wall-thickening and enhancement or

wedge-shape low-attenuation parenchymal lesions due to delayed excretion. As in the case of obstructive uropathy, the entire kidney may demonstrate delayed enhancement due to more central obstruction.

Other types of calcification include staghorn calculi that fill and outline the renal pelvis and calyces. Calcifications of the kidney and bladder can also be seen in inflammatory or infectious processes such as TB and even in RCC, but in the setting of RCC, an associated abnormal enhancing soft tissue mass is typically present. Hilar calcifications on unenhanced CT may be vascular in etiology and should be suspected in the setting of calcific atherosclerosis. These should not be confused with renal calculi.

Cystic Renal Lesions

Hydronephrosis or dilatation of the pelvocalyceal systems should be differentiated from parapelvic cysts. On unenhanced CT this may be difficult. Communication between the fluid-filled structures within the kidney is indicative of hydronephrosis. Postcontrast urograms are also useful to separate collecting system and calyces from cysts. If obstruction is suspected, one should try to find the point of obstruction. Calyceal diverticula may be seen and can be differentiated from cysts on delayed postcontrast imaging as these lesions communicate with the collecting system and will fill at least partially with contrast in the dependent portion of the diverticulum. Unenhanced imaging should be reviewed to ensure that milk of calcium or calcification in a cyst is not mistaken for contrast as both may be similar in density. Multiple cysts can be seen incidentally or in polycystic kidney disease, which may also be associated with polycystic liver disease, tuberous sclerosis (TS) and Von Hippel-Lindau Disease (VHL).

TS is an autosomal dominant disorder leading to mental retardation, seizures, and cutaneous lesions. Multiple angiomyolipomas (AML) are seen more frequently in these patients.

VHL is another autosomal dominant hereditary disease and kidney manifestations include multifocal renal cell

carcinoma and cysts. Pheochromocytomas, pancreatic adenomas, islet cell tumors, and hemangioblastomas of the brain and spinal cord are other manifestations of this systemic disease.

Simple cysts are common. Introduced in 1986, the Bosniak CT classification criteria remain a useful radiologic tool for differentiating between surgical and non-surgical lesions and will be reviewed briefly (Table 1) (44). Category I lesions are benign, simple cysts defined as fluid density, unilocular lesions with a thin, nonenhancing wall. No calcification or septations are present. Category II (Fig. 8) are minimally complex benign lesions with a few hairline septations of fine nonenhancing septations. Small (<3.0 cm) hyperdense cysts also fall in this category. Category IIF is a subset of lesions that require follow-up as they are slightly more complex but not considered surgical lesions as are category III. These lesions are thought to be benign and may contain increased number of thin or minimally thickening septations or contain thick or nodular calcification but no enhancing soft tissue component. They also include greater than 3 cm intrarenal hyperdense cysts. Category III lesions are indeterminate and considered surgical lesions although 50% of these lesions are benign. They have thickened or irregular enhancing walls or septations which may contain calcification. Category IV cysts include malignant lesions that contain enhancing soft tissue elements. Unenhanced and enhanced CT imaging, as stated above, are required for classification. Small, less than 1-cm cysts may be impossible to characterize on CT unless thin section imaging is obtained.

Solid Masses

Fat containing

AML are benign hamartomas composed of variable amounts of fat, smooth muscle, and blood vessels (Fig. 9). They occur more frequently in women and patients with TS. AML is distinct from other renal tumors

Table 1 Bosniak Criteria for Evaluation of Renal Cystic Masses

Category	Diagnosis	Features
Category I	Benign simple cyst, nonsurgical	Unilocular, fluid density, thin, nonenhancing wall
Category II	Complex benign lesions, nonsurgical	A few hairline septations, nonenhancing; also small (<3.0 cm) hyperdense cysts
Category IIF	Require follow-up, nonsurgical	Increased number of thin or minimally thickening septations; thick or nodular calcification; no enhancing soft tissue component; also >3 cm intrarenal hyperdense cysts
Category III	Indeterminate, surgical	Thickened or irregular enhancing walls or septations; may contain calcification
Category IV	Malignant, surgical	Enhancing soft tissue elements

Source: From Ref. 44.

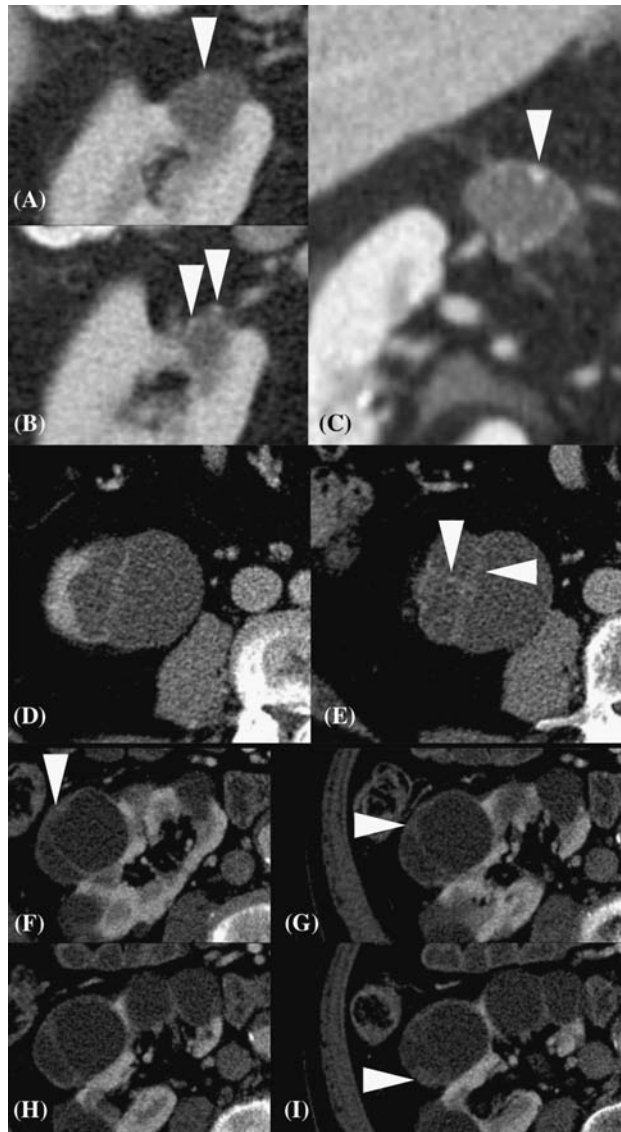


Figure 8 Cystic lesions of the kidney. (A–C) Bosniak II cyst due to partial punctuate calcification (*arrowheads*). (D–E) Bosniak IIF cyst with multiple septa and perceived 1–2 mm enhancing septations (*arrowheads*). (F–I) Bosniak III cyst. Thickened irregular wall with nodular mild enhancement compared with noncontrast images (*not shown*).

because of the presence of fat in lipid rich AMLs which is easily detected on CT imaging. Unenhanced CT reveals variable amounts of soft tissue and fat (<30 HU) and tend to be slightly hypoattenuating to renal parenchyma while enhanced CT will reveal enhancement in the soft tissue elements. Dilated aneurysmal vessels are also seen in AMLs. This feature makes AMLs susceptible to hemorrhage which can be life threatening. Large AMLs are typically followed with routine imaging and if they grow larger than 3.5 or 4 cm, intervention may be warranted because of an increased risk of hemorrhage. Lipid-poor

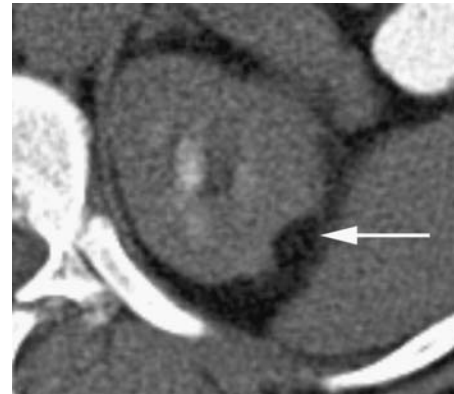


Figure 9 The presence of fat density within this small lesion (*arrow*) is pathognomonic for angiomyolipoma.

AMLs may mimic a malignant neoplasm since no detectable fat may be present. Depending on the size of the lesion and clinical factors, close interval follow-up or surgical resection may be warranted to exclude malignancy. If calcification is present with a fat-containing mass, renal cell carcinoma should be considered, as AMLs do not contain calcium. Some larger RCCs may contain small amounts of fat also, although this is rare.

Nonfat containing solid renal masses

Oncocytomas are benign renal tumors indistinguishable from renal cell carcinoma on imaging. Thus, they are surgical lesions based on imaging criteria. They are solid well-circumscribed lesions isoattenuating to hypoattenuating relative to normal renal parenchyma and enhance homogeneously or in a spoke wheel-like pattern on early phase imaging. A central low attenuation scar may be present that may mimic central necrosis that can also be seen in RCC.

Pseudotumors

Pyelonephritis and renal abscesses may be mistaken for neoplasm. Pyelonephritis typically causes a striated nephrogram because of patchy delayed excretion with wedge-shaped low attenuation regions in the cortex. The process tends to be bilateral but may be unilateral because of ascending infection and may be associated with bladder wall thickening. Focal pyelonephritis and abscesses may mimic carcinoma appearing as solid masses. Abscess may develop central low attenuation due to necrosis. Antibiotic therapy may be warranted in the appropriate clinical setting with follow-up imaging to assess to interval decrease in size. Infection should respond to antibiotics, whereas a neoplastic process should not alter in size at short-term follow-up. Biopsy may be warranted if lesion is still indeterminate. Emphysematous cystitis, pyelitis, or pyelonephritis may occur with air in the wall of the bladder, collecting system, or kidney, respectively,

indicating a serious infection more often seen in diabetic patients. However, air may also be introduced into the urinary tract following intervention, and a clinical history of intervention should be elicited. Renal congenital dysmorphism and cortical scarring due to prior infection or infarct may distort the contour of the kidney and be mistaken for a mass particularly on unenhanced CT. Hematoma, inflammatory lesions, vascular lesions, and dilated calyces may also mimic renal masses (44). Dynamic contrast-enhanced imaging CT or MRI as well as clinical correlation is advised to better distinguish between true renal lesions and pseudomasses prior to intervention.

Lymphoma

Lymphoma may spread to the kidney via direct extension or hematogenous spread. Multifocal lesions may be present or the kidney may become enlarged if infiltrated with lymphoma. Biopsy is helpful particularly in the setting of multifocal enhancing lesions as the differential includes infection, lymphoma, multifocal RCC, and metastases.

Metastatic disease

Metastases to the kidney are most commonly from lung primaries and tend to be multiple, bilateral, and associated with other organ involvement. They may be discrete masses or infiltrative lesions. Multifocal RCC or oncocytomas can occur, however, and should be differentiated from metastases. Solitary renal metastases will look similar to RCC on imaging but should be considered in the differential diagnosis in patients with a history of malignancy that is known to metastasize to the kidney.

RCC

RCC is the most common renal neoplasm and is variable in appearance ranging from solid to cystic with papillary projections. The lesion may be well circumscribed or infiltrative and tends to be heterogeneous in enhancement with central low attenuation within it because of necrosis, particularly, in larger tumors. These tumors tend to be hypervascular, a feature seen in metastatic renal cell carcinoma as well, but there is a wide range of enhancement patterns. RCC tends to invade the renal veins and inferior vena cava and may extend into the right atrium (Fig. 10). Local regional metastases may be present and are associated with a poorer prognosis. Direct invasion of adjacent organs can occur and metastases may be seen to the adrenal, contralateral kidney, liver, lung, and bone.

Postoperative kidney

Radical nephrectomy with or without adrenalectomy was the mainstay of treatment for RCC in the past, but today there are other options. Total nephrectomy may still be indicated but may be performed with either open or

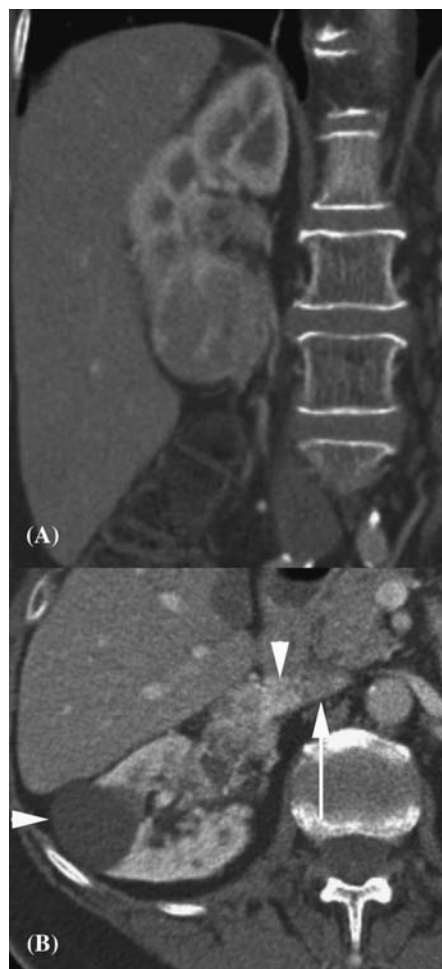


Figure 10 Primary renal cell carcinoma invading the renal vein. Coronal (*above*) and transaxial (*below*) contrast-enhanced CT during the portal-venous phase demonstrates a large right renal mass at the lower pole with a thickened irregular wall and septa with an enhancing soft tissue component independent of the wall or septa which in this case is invading the right renal vein (*vertical arrowhead*), extending to the inferior vena cava (*arrow*). Note the benign-appearing Bosniak I renal cyst (*horizontal arrowhead*).

laparoscopic procedures. Hernia of fat and bowel may be seen as a result of surgery and the bowel and pancreas may fall into the postoperative bed, mimicking recurrence. Postoperative clips and stranding may be seen in the postoperative bed as well and this may be normal.

Increasingly, nephron-sparing surgery or partial nephrectomy is performed using an open or laparoscopic technique. This procedure tends to result in a focal renal parenchymal defect sometimes occupied by fat-packing. Postoperative gas, fluid density, or higher density collections may be seen in the immediate postoperative bed which will most often resolve over time. If gas is present in the postoperative bed after one week of surgery infection should be considered. Hematomas may also develop

as a complication with displacement of the kidney by a heterogeneous hyperattenuating mass on unenhanced and enhanced CT but no enhancement should be present. Urine leaks can occur and this may only be apparent on delayed contrast-enhanced CT on the excretory phase of imaging. On unenhanced imaging, urine leak may appear as a nonspecific fluid density collection.

The postpartial nephrectomy kidney will be smaller in size and slightly abnormal in contour. Recurrence is more likely to occur after six months to 1 year. Enhancing soft tissue with nodularity should raise concern for recurrence. Enhancing granulation tissue or fibrosis may occur but should appear smooth in contour and decrease or remain stable over time. Serial imaging is used to assess for interval change.

Other treatments such as radiofrequency ablation and cryotherapy may be used as well. RF ablation will lead to necrosis within the tumor, often with reduction in size. The tumors may become fluid density or may remain hyperdense due to scarring but should not demonstrate internal enhancement. Hemorrhage may occur which may lead to an increase in size of the lesion but no enhancement should be present. Rim enhancement may be present but should resolve over time.

PET and PET/CT Imaging of RCC

Initial diagnosis

In 1991, Wahl and coworkers demonstrated in five patients that RCC primary tumors and metastases accumulated FDG (45), setting into motion the further study of this tracer for RCC. In 1996, Bachor found the FDG uptake was increased in 20 of 26 primary tumors (Fig. 11). False positives included an angiomyolipoma, a pericytoma, and a pheochromocytoma. Three out of three patients with lymph node metastases had positive findings on PET (46).

In 1997, Goldberg employed FDG PET with Lasix diuresis to study 10 malignant renal tumors and 11 patients

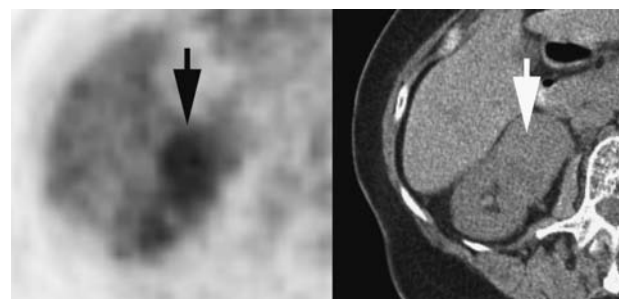


Figure 11 In contrast to small renal carcinomas which can be falsely negative on PET, this large lesion is clearly FDG avid (vertical black arrow). Note heterogeneous density on CT (white arrow) that can be appreciated even without IV contrast. Abbreviation: IV, intravenous.

with Bosniak type 3 indeterminate renal cysts. PET identified the renal tumors with 90% sensitivity and all but one indeterminate cyst was correctly classified as benign with no false-positive interpretations (47).

In 2001, Ramdave found an overall accuracy of 94% for both PET and CT in the characterization of suspected primary renal tumors. PET altered treatment in 6 of 25 patients because of confirmation of benign pathology or upstaging of unsuspected metastatic disease. Treatment changes were made because of PET in four of eight patients with suspected recurrence or metastasis by upstaging three patients and excluding recurrence in one (48).

As is often the case, the early promising results looking at FDG PET for RCC have not been confirmed by larger, prospective trials. In 2003, Aide and coworkers prospectively examined patients with suspicious renal masses by CT and PET. Among 18 patients imaged because of a suspicious mass, sensitivity was only 47% with a specificity of 80% and an accuracy of 51% (Fig. 12) compared with 97%, 0% (5 false positives and no true negatives), and 83% for CT (49).

Kang and coworkers echoed these less-than-encouraging findings in a study published in 2004. Among 66 patients

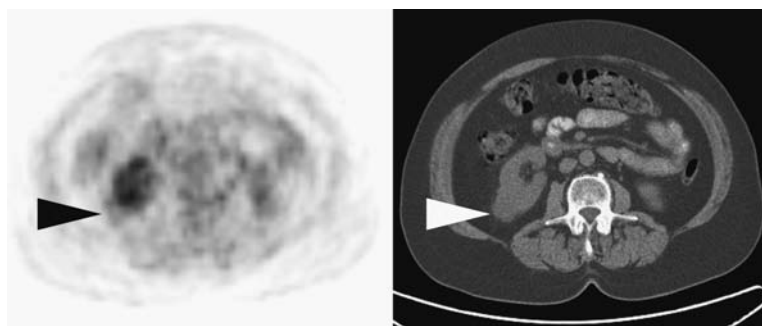


Figure 12 Low-grade uptake in renal cell carcinoma. This tumor has only mild to moderate FDG uptake (arrows) that is much reduced compared with adjacent physiologic renal activity.

with known or suspected primary RCC, FDG PET resulted in a sensitivity of 60% and a specificity of 100% for primary RCC tumors compared with 92% and 100% for CT. Clearly no advantage was identified for characterization of the primary lesions (50). In a smaller, more recent study, Ak and coworkers examined 19 patients with suspicious renal masses and found a sensitivity, specificity, and accuracy of 86%, 75%, and 84% for the characterization of the primary lesion (51).

In summary, early studies suggested a possible role for FDG PET in characterizing renal masses but more recent work has in general demonstrated reduced sensitivity with PET and overall improved accuracy with CT. FDG PET in its current form is unlikely to offer a specific advantage over CT or MRI except perhaps in equivocal cases.

Detection of metastases

Although current opinion suggests that FDG PET is not successful for characterizing primary tumors, the data is somewhat more encouraging for detection of metastases, especially when compared with the performance of CT. An early report in 1996 found three of three nodal metastases with FDG PET (46), and another early study demonstrated FDG PET detection of a bone metastasis that was negative on bone scan (52). In a larger study of 18 patients with biopsy-proven RCC, Wu found that FDG PET detected osseous metastases with 100% sensitivity and specificity compared with 78% and 60% for bone scintigraphy (53).

In 2003, Aide and coworkers performed a more extensive analysis of the ability of FDG PET to detect metastases just before or after initial surgery to remove the

primary tumor. In 16 patients with metastatic disease, FDG PET detected all lesions seen by CT and also identified eight additional sites leading to an accuracy of 94% for PET versus 89% for CT in the initial staging of RCC. The authors suggest that PET may be useful if a single metastasis or equivocal lesion is seen at CT (49).

FDG PET has been used to study indeterminate lung nodules in patients with RCC (Fig. 13). In 2003, using an SUV cutoff of 2.5 Chang found that FDG PET correctly identified nine true-positive lung lesions and four true-negative lesions with one false positive and one false negative (54). FDG PET may therefore be indicated in patients with equivocal pulmonary nodules on chest X ray (CXR) or chest CT.

Other studies have not found such success with FDG PET in the detection of metastases. Majhail and coworkers examined 36 sites of distant metastatic disease suspected on CT or MRI with FDG PET and documented histology at 33 sites. PET performed with a sensitivity, specificity, and positive predictive value of 64%, 100%, and 100%. False-negative lesions had an average size of 1 cm compared with true-positive lesions that, on average, measured 2.2 cm. They suggest that although of limited value, FDG PET may be useful to avoid biopsy in suspicious lesions on CT or MRI that are definitively abnormal on PET (55).

Kang also compared PET with CT in the detection of metastases with similar results. In a study of 66 patients, PET performed with a 75% sensitivity and a 100% specificity compared with 93% and 98% for CT in the detection of retroperitoneal lymph node metastases and/or renal bed recurrence. Metastases to the lung parenchyma were detected with 75% sensitivity and 97% specificity compared with 91% and 73% for CT, suggesting that PET/CT might be the most optimal study for the characterization of lung lesions. Similarly, PET was less sensitive but more specific than CT in the detection of bone metastases. The authors concluded that PET may be useful when conventional imaging was equivocal (50). Others have confirmed a lower sensitivity and higher overall specificity for the detection of metastases and some have suggested the use of PET prior to surgery to remove metastases in order to detect any other lesions that would change management (56).

In conclusion, PET is of uncertain value compared with CT for the detection of RCC metastases. It does have the ability to detect additional lesions and may be useful to search for additional tumor before deciding on definitive treatment in patients with recurrent disease.

Treatment response

Few papers specifically examine the value of FDG PET in treatment response for RCC. In 1997, Mankoff reported that FDG PET was useful to identify a complete response

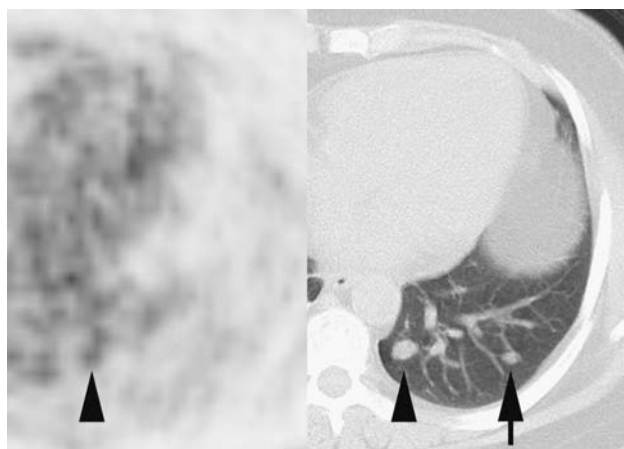


Figure 13 Low-grade FDG uptake in renal cell carcinoma metastases. Even this moderately large 1.2×0.8 cm pulmonary metastasis of renal cell carcinoma (arrowheads) demonstrates only mild to moderate FDG uptake equal to the mediastinal blood pool. The smaller lesion on the same CT slice (arrow) is not detectable on PET.

to interleukin-2 therapy in a patient with persistent radiographic evidence of tumor (57). Jennens demonstrated that FDG PET predicted response to samaxanib therapy in RCC (58). Further studies are required to more clearly define the role of FDG PET in the monitoring of treatment response for metastatic RCC.

Other tracers

In 1995, Shreve demonstrated reduced washout of ^{11}C -acetate in renal cancers relative to non-neoplastic renal tissue (59). Unfortunately, in a clinical trial of 21 patients with this tracer, overall uptake in renal tumors was low and the tracer was not recommended for the characterization of a renal mass (60). The amino acid proline has been fluorinated and studied using PET for detection of renal carcinoma with disappointing results (61). More encouraging findings have been shown with an ^{124}I -labeled antibody against an enzyme (carbonic anhydrase-IV) that is overexpressed clear-cell renal carcinomas. Researchers found in 26 patients with renal masses that PET using this tracer was able to detect clear-cell histopathology with a 94% sensitivity and a 90% negative predictive value. They argue that preoperative identification of this histological subtype may affect treatment (62). Further studies are required to determine if a clinical application for this antibody emerges.

Conclusions Regarding CT, PET, and PET/CT in Renal Cell Carcinoma

PET and PET/CT currently has a limited role in the initial diagnosis of renal cell carcinoma due to low FDG uptake within many primary tumors with a subsequent low overall sensitivity. PET or PET/CT does have the potential to detect more metastases in patients with aggressive primary tumors and its role needs to be clearly defined in this regard. PET or PET/CT has an emerging role in treatment response. Investigational agents show promise but must be further tested.

UROTHELIAL CANCER

The vast majority of urothelial cancers are transitional cell carcinomas, which occur most frequently in the bladder followed by the renal pelvis and rarely the ureter. The AJCC predicts an incidence of 67,160 new cases and 13,750 deaths from bladder cancer in 2007. Only 2,050 tumors of the ureter and other urinary organs will be diagnosed and there will be 700 deaths (1). Patients with urothelial carcinomas typically present with hematuria or urinary frequency (63). Bladder and ureteral cancer is usually diagnosed by cystoscopy, and tumors of the renal pelvis can be characterized on ultrasound, CT, or MR.

Conventional Management and Imaging of Bladder Cancer

Cystoscopy is the most commonly employed method to evaluate suspected bladder cancer. In cases where there is a papillary lesion or visual evidence of tumor limited to the mucosa, localized surgery is sufficient for treatment and no radiological imaging is recommended. In the case of possible muscle invasion or other aggressive features, CT imaging of the abdomen and pelvis has been traditionally recommended before transurethral resection of the bladder tumor. When invasive disease is confirmed after surgery, upper tract evaluation under anesthesia using cystoscopy is also recommended, given the frequency of synchronous primary tumors in the upper tract in patients with bladder cancer. Chest CT and bone scans are typically recommended in this situation (64).

CT imaging for staging of bladder cancer is typically performed using a three-phase protocol, including a non-contrast scan through the abdomen or abdomen and pelvis followed by a contrast enhanced study at approximately 90 seconds followed by a delayed phase at approximately 10 minutes to visualize tracer within the renal collecting system, ureter and bladder. A three-phase protocol allows for optimal detection of small enhancing or nonenhancing intraluminal lesions and permits assessment of other potential causes of hematuria such as renal stones and renal cell carcinoma (Fig. 14). Three-dimensional reconstructions provide additional information but do not replace careful review of transaxial images. Prone imaging, saline bolus, IV administration of furosemide or application of abdominal compression can also be useful during imaging to distend the urinary system and enhance lesion detection (64).

TCC is the second most common renal neoplasm and can concomitantly occur in the bladder and ureter, but most commonly in the bladder. Squamous cell carcinoma is most frequent. Unenhanced CT may reveal a polypoid mass in the bladder or signs of obstruction such as hydronephrosis, renal atrophy from chronic obstruction, or enlargement if acutely obstructed with a mass seen at the point of transition (Fig. 15). Delayed renal enhancement may be present secondary to obstruction. The mass may be hyperattenuating because of the presence of hemorrhage or calcification. On contrast-enhanced CT, the mass will enhance unlike blood clot or pus.

If TCC is suspected the entire genitourinary system should be assessed with CT, or, if patient has renal function impairment, MR urography, particularly to assess the upper tract to look for additional foci of tumor and metastatic disease. Urine cytology and cystography are most helpful for confirmation of diagnosis. Direct extension to the pelvic sidewall and metastases to lung and bone may occur.

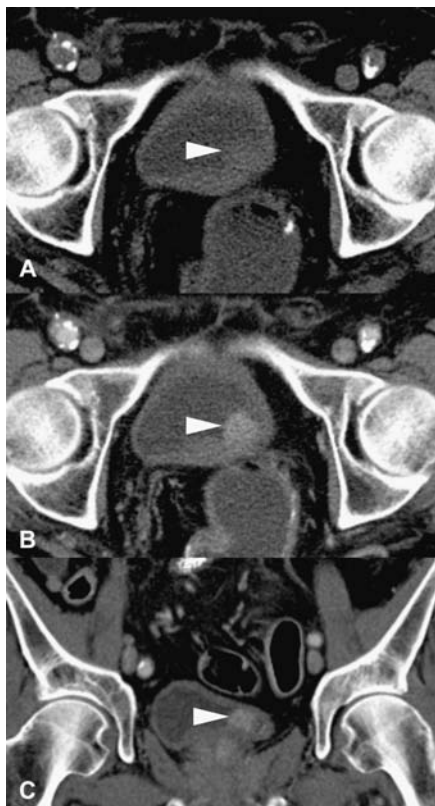


Figure 14 Transitional cell carcinoma of the bladder. (A) Noncontrast-enhanced CT demonstrates a very subtle lesion in the bladder that enhances and is more clearly seen on (B) the transaxial and (C) coronal reconstructions from the subsequent contrast-enhanced study.

The CT appearance of primary bladder cancer is variable and can appear as papillary, sessile, infiltrating, mixed, or flat lesions lining the bladder epithelium. Lesions frequently enhance on multiphase CT. Perivesical

fat infiltration is suggestive of advanced disease but false positives can be seen following biopsy or surgery. Local staging is reported to be only 60% to 83% accurate with CT. Accuracy for lymph node staging ranges from 73% to 92% with understaging being a significant concern. CT can also be useful for detection of recurrent disease that commonly occurs in the bones, lungs, brain, and liver. Posttreatment imaging is complicated by postoperative findings that can be difficult to characterize (64).

MRI has significantly advanced in recent years for the imaging of bladder cancer. It offers better staging of the primary tumor because of increased soft tissue contrast and early reports have also suggested an advantage in terms of local nodal staging. Disadvantages include inability to detect air and stones in the urinary system and decreased resolution for imaging of the upper urinary tract (64).

Conventional Imaging of Upper Tract Urothelial Cancer

Similar to bladder cancer, upper tract urothelial carcinomas are best imaged using CT urography. In this case, the study is typically used to identify and characterize disease in patients with hematuria or other symptoms concerning for a renal or urinary neoplasm.

Upper tract urothelial carcinomas typically appear as enhancing, focal, nodular intraluminal soft tissue densities that appear as a filling defect on delayed images. TCC may also present as a renal mass rather than an intraluminal filling defect mimicking RCC. The enhancement is typically less than the surrounding kidney and it may appear more homogenous than RCC. TCC does not invade the venous system but can obliterate calyces due to invasion. TCC may also present as wall thickening rather than a mass that may be concentric or eccentric. Infection, inflammatory disease, endometriosis, benign, and metastatic

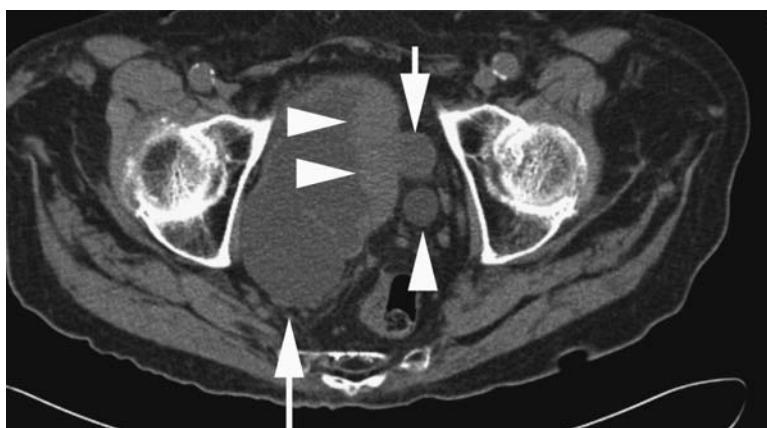


Figure 15 Primary bladder cancer on CT. Unenhanced CT image demonstrates a lobulated solid mass in the wall of the bladder (horizontal arrowheads). Note also bladder diverticuli (arrows) and a dilated left ureter (vertical arrowhead) due to partial obstruction.

disease to the ureter have a similar appearance. There may be invasion into the perirenal fat and associated lymphadenopathy. In the ureter, these lesions can appear as segmental urothelial thickening with narrowing of the lumen and enhancement. These findings can be associated with signs of urinary obstruction. Benign strictures can mimic upper tract tumors and lead to false positives. Tumors typically measure approximately 30 HU compared with blood clot and calculi which usually measure 50 to 75 HU and greater than 100 HU, respectively. Equivocal lesions can be followed over time with repeat CT studies. In general, CT urography is useful to differentiate T1 and T2 tumors from more advanced stage primary lesions that invade peripelvic fat or renal parenchyma and can also identify T4 disease, which is characterized by the invasion of adjacent organs or extension through the renal parenchyma into the perinephric fat. CT can also be used to detect common sites of distant metastatic disease including the lymph nodes, liver, bones, and lungs (Fig. 16) (65).

PET/CT for Urothelial Cancer

Initial Diagnosis

There are no studies directly examining the ability of PET to detect undiagnosed bladder cancer. However, a 1997 study by Kosuda demonstrated a 60% sensitivity for

detection of residual primary tumor after initial therapy, and, therefore, it may be theoretically possible to detect incidental undiagnosed bladder cancers (66). The high urinary excretion of FDG typically limits the utility of PET for detection of primary bladder tumors. However, Kamel and coworkers have demonstrated successful detection of intravesical lesions by means of forced diuresis (67), and a similar protocol has been reported successful in the identification of one case of high-grade lymphoma in the bladder (68). It remains to be seen whether or not such techniques might become useful in the routine initial diagnosis of bladder cancer. It will be difficult to improve upon the accuracy of direct visualization imparted by cystoscopy.

Initial Staging

Following biopsy or resection of the primary tumor, often by a transurethral approach, it becomes important to determine the local extent of the primary tumor and find any local or distant metastases. In 1999, Bachor examined 64 patients preoperatively with FDG PET. Among 21 patients with lymph node metastases found in the pelvis at surgery, PET identified 14 of them. Sensitivity was 67%, specificity 86%, and accuracy 80%. The authors concluded that FDG PET was probably superior to CT for detection of pelvic lymph node metastases (Fig. 17). Heicappell also found a sensitivity of 67% in a small

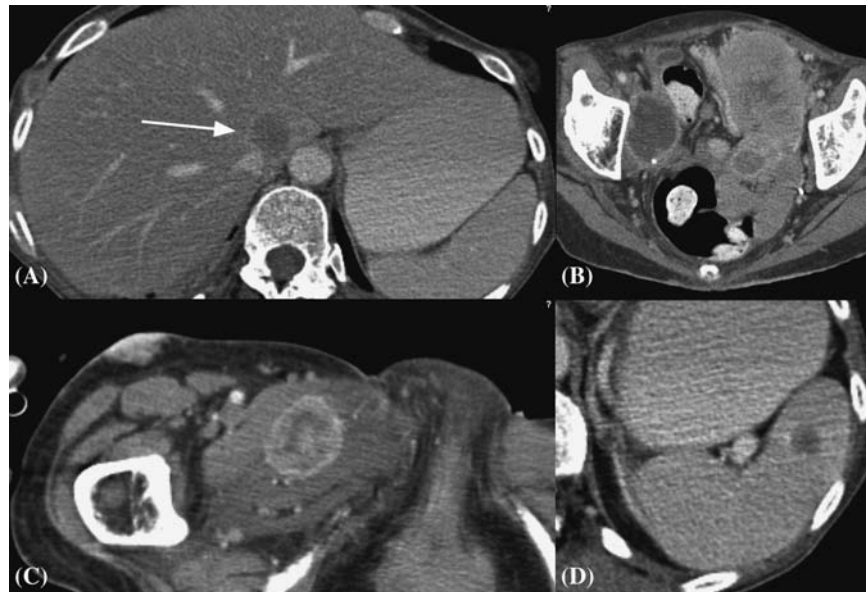


Figure 16 (A) Liver metastasis of bladder cancer. IV contrast-enhanced diagnostic CT during the portal-venous phase demonstrates a hypoattenuating lesion in the caudate lobe (*arrow*) because of bladder cancer. (B) Peritoneal metastasis of bladder cancer. IV contrast-enhanced CT demonstrates a large heterogeneous mass in the left lower pelvis. Central hypodensity is suggestive of hemorrhage or necrosis. (C) Bladder cancer muscle metastasis on CT. IV contrast-enhanced study demonstrates a well-circumscribed round heterogeneous mass with peripheral enhancement. (D) Splenic metastasis of bladder cancer. IV contrast-enhanced CT demonstrates a hypoattenuating lesion in the liver due to metastatic disease. *Abbreviation:* IV, intravenous.

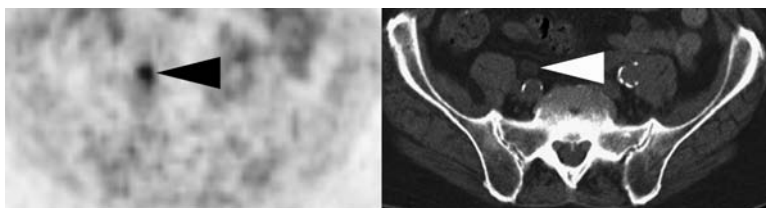


Figure 17 Subcentimeter lymph node metastasis of bladder cancer detected by PET/CT. Focal intense FDG uptake (*black arrowhead*) corresponds to a metastatic right common iliac lymph node that would not be considered pathological on CT alone (*white arrowhead*).

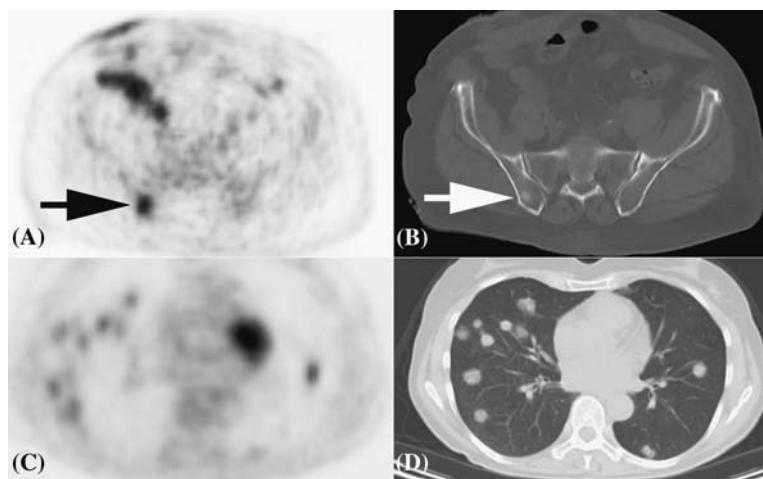


Figure 18 Viable bone metastasis of bladder cancer detected by PET/CT. (A) A morphologically stable sclerotic metastasis on CT (*white arrow*) remains metabolically active (B) on PET after chemotherapy (*black arrow*). CT alone could not determine the presence of residual tumor. Lung metastases from bladder cancer on PET/CT. (C) Intense FDG uptake is noted in several large pulmonary lesions seen on CT (D).

study in which PET detected two out of three patients with local lymph node metastases before surgery (69). In a more recent study, Drieskens found a sensitivity of 60% with a specificity of 88% and an accuracy of 78% for the detection of all metastases in a study of 40 patients who underwent PET that was simultaneously interpreted with separately acquired CT. The authors noted that PET was most useful for the detection of distant metastases (Fig. 18) and that sensitivity for detection of local nodal metastases remained low at 60% (70). In conclusion, PET or PET combined with separate CT is of limited sensitivity for the detection of local nodal metastases and therefore cannot replace lymph node dissection in patients at risk for metastases. It may be useful for the detection of occult distant metastases preoperatively in patients with sufficiently high risk of occult stage-IV disease.

Recurrence Detection

There is very limited literature examining the ability of FDG PET or PET/CT to detect recurrent bladder cancer. In 1997, Kosuda reported that FDG PET was able to detect 17 distant metastatic lesions and two of three

regional lymph node metastases in 12 patients with bladder cancer who had undergone surgery or radiotherapy (66). This preliminary data suggested a possible role of FDG PET in restaging bladder cancer.

In 2006, Liu reported that FDG PET had only a 50% sensitivity in the detecting residual primary tumor after chemotherapy (71). Anjos reported more encouraging results by combining FDG PET with forced diuresis. In 17 patients previously treated surgically for bladder cancer, FDG PET combined with diuresis and delayed imaging detected recurrent bladder lesions in six patients, pelvic lymph node metastases in two individuals and a single prostate metastasis. Seven of 17 patients were upstaged by PET using delayed scan with diuresis (72). This study suggests a possible useful role of FDG PET in detecting recurrent bladder cancer that is enhanced by forced diuresis. Further studies are required to more precisely define the role of FDG in recurrence detection.

Treatment Response Monitoring

There are no studies directly examining the utility of FDG PET or PET/CT in treatment-response monitoring. In

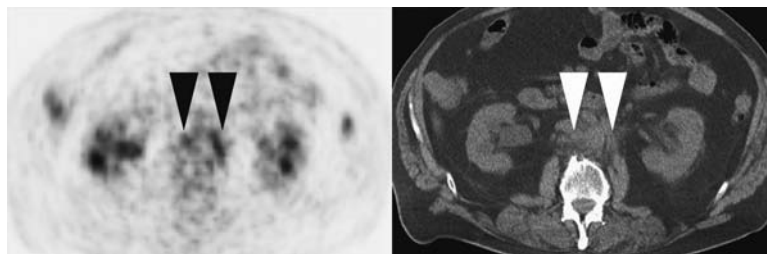


Figure 19 Active bladder cancer metastases after therapy on PET/CT. Intense FDG uptake in residual metastatic retroperitoneal lymphadenopathy is seen following chemotherapy, prompting the referring physician to continue treatment.

patients with advanced disease that is detectable on FDG PET, it should be possible to monitor response to chemotherapy with this modality (Fig. 19). Well-designed studies are required to prove its value, and, until then, one must rely on PET's capability for evaluating treatment response in other cancers as a justification for its use in advanced bladder cancer.

False Positives

Few case reports have addressed the issue of false-positive findings. Pirson has reported a false-positive PET result in a patient with a bladder diverticulum (73). Careful review of CT images on current PET/CT scanners should overcome this potential limitation. Others have reported false-positive uptake of tracer in the dependent portion of the bladder after diuresis and proposed that additional prone imaging in this situation can eliminate this pitfall (74). The author of this text has noted that focal distal ureteral activity can at times be problematic when lymph nodes or postoperative changes are in close proximity to sometimes poorly visualized ureters. Delayed PET/CT imaging following hydration and voiding using a lower CT dose to limit radiation exposure has proven useful.

Other Tracers

Several investigators have examined the utility of other tracers in an attempt to circumvent the problems associated with intense accumulation of FDG in the urinary bladder. In 1994, Letocha and coworkers evaluated ^{11}C -methionine in patients with muscle-invasive transitional cell carcinoma of the bladder and found poor diagnostic accuracy (75). In 1996, Ahlstrom was able to visualize 18 of 23 primary bladder cancers with ^{11}C -methionine, but concluded that its value in staging was not improved compared with conventional methods (76).

In 2002, de Jong and coworkers reported on the value of ^{11}C -choline PET for visualization of primary bladder cancers before surgery. They reported low uptake in the normal bladder and high uptake in 10 primary tumors with an SUV of 4.7 ± 3.6 . One false positive was found in a patient with an indwelling catheter. In situ carcinoma,

dysplasia and noninvasive urothelial tumors were all undetected (77). Four years later, Gofrit reported on the use of ^{11}C -choline PET/CT in 17 patients with bladder cancer and two patients with upper tract transitional cell carcinomas. All patients had negative CT scans before surgery. Choline PET/CT found all primary transitional cell carcinomas with an average SUVmax of 7.3. Interestingly, all three refractory in situ bladder carcinomas were visualized and six patients demonstrated nodal uptake within lymph nodes as small as 5 mm. Four patients underwent surgery and three were found to have nodal metastases. Bone metastases were also visualized on PET. The authors concluded that choline PET is very promising for the imaging of transitional cell carcinoma (78). Further evidence supporting the value of choline PET was provided by Picchio and coworkers in a similar study that found a 96% sensitivity in the detection of residual primary tumor (compared with 84% for CT), 62% sensitivity in the detection of lymph node involvement (compared with 50% for CT), and no false-positive lymph nodes (compared with 22% false positive on CT). Both modalities missed small peritoneal metastases found at surgery but the authors conclude that overall choline PET was more accurate than CT for the staging of bladder cancer (28). In summary it appears that ^{11}C -methionine is not a useful tracer for urothelial cancer but ^{11}C -choline is very promising, likely more accurate than CT, and may become more useful in the future if this tracer becomes more readily available. Fluorinated thymidine is also currently under investigation and has been used to image a renal transitional cell carcinoma within a benign cyst (79).

Conclusions Regarding PET and PET/CT in Urothelial Cancer

PET and PET/CT currently have a limited role in the diagnosis of urothelial cancer due to high urinary background activity. The PET/CT reader should, however, be aware of the CT and PET appearance of occasional urothelial cancers that will be incidentally seen. PET and PET/CT are of limited value in the initial nodal staging of urothelial cancer and cannot replace lymph-node biopsy at surgery. FDG PET or PET/CT may have a

possible role in recurrence detection if used with diuresis, but further studies are required to define its role. ¹¹C-choline PET may be useful in detecting primary tumors and metastases and requires further study.

TESTICULAR CANCER

Background

Testicular cancer represents 1% of all malignancies in men. The American Cancer Society has predicted 7,920 new cases of testicular cancer in the United States in 2007. Fortunately, most cases of testicular cancer are highly curable by orchiectomy, and only 380 deaths have been predicted for the same year (1). The majority of malignant testicular neoplasms arise from germ cells and include seminomas, embryonal carcinomas, teratomas, yolk sac tumors, and, rarely, choriocarcinomas. Forty percent of germ cell tumors present as mixed histological subtypes, typically with teratoma combined with other subtypes. Sixty percent of germ cell tumors are pure seminomas (80).

Initial diagnosis of testicular cancer is generally achieved by palpation of a testicular mass. Although monthly testicular self-exams are generally recommended by health care professionals, there is no data to support screening programs for testicular cancer. The low incidence and highly treatable nature of this disease present a challenge for investigators wishing to find any benefit to screening.

Conventional Imaging

Testicular cancer typically presents as a palpable mass. The primary radiological modality for evaluation of a testicular mass is scrotal ultrasound. Ultrasound can differentiate neoplastic from non-neoplastic lesions in the scrotum (such as cysts) and can determine if a mass is intratesticular (likely malignant) versus extratesticular (more likely benign). MRI has limited clinical utility for the evaluation of testicular cancer and is currently under investigation. Intratesticular tumors typically require orchiectomy for definitive diagnosis.

CT for Testicular Cancer

Initial staging

Staging of testicular cancer is typically performed with CT following confirmation of tumor at orchiectomy. Proper selection of therapy options including surveillance, radiation therapy, or chemotherapy depends on accurate staging, with particular emphasis on the status of the abdominopelvic lymph nodes. Separating the majority of patients with no metastases from the smaller populations of individuals who do harbor disease (13–19% of patients

with seminoma, 24–30% of those with nonseminoma) (81) would be very useful for selecting the appropriate therapy.

In 1995, Moul examined the efficacy of CT in the detection of metastatic testicular cancer after orchiectomy. Fifty-seven patients underwent CT after diagnosis of the primary tumor and were subsequently treated with retroperitoneal lymph node dissection. Overall accuracy for CT in predicting nodal status was 67% with a 33% false-negative rate. The authors also determined that CT of the chest was only useful in patients with the disease identified in the abdomen. There was a high false-positive rate in the chest in patients with no nodal metastases in the abdomen, and CXR was considered equivalent to CT in these patients. The authors reported that other clinical parameters including volume of embryonal carcinoma and immunohistochemical findings were more predictive of the disease stage (82).

In 1995, Leibovitch used a 3-mm cutoff for the CT staging of retroperitoneal lymph nodes in patients with low-stage nonseminomatous germ cell cancer with a sensitivity and negative predictive value of 90% (83). Two years later, Hilton noted a sensitivity of 37% and a specificity of 100% using a 1-cm cutoff in clinical stage I nonseminomatous germ cell cancer and a sensitivity of 93% with a specificity of 58% using a 4-mm criterion (84).

Restaging seminoma

Follow-up CT scanning after initial surgery and adjuvant therapy is intended to detect clinically inapparent recurrent lymph node metastases, lung or liver metastases, or less common sites of distant disease. In patients with stage I disease, follow-up abdominopelvic CT has been recommended starting every three months for the first year followed by decreasing frequency for a total of 10 years. CXRs have also been recommended with slightly lower frequency (81). In patients with stage II or III seminoma, the most common finding on CT is a residual soft tissue mass. Prior to the advent of PET, abdominopelvic CT follow-up of these lesions was recommended to document stability in addition to follow-up CXRs. Clinical practice varies with some institutions removing lesions greater than 3 cm while other lesions simply follow these tumors to determine stability.

Restaging nonseminoma

In 2002, Harvey and coworkers examined the efficacy of CT in the follow-up of patients with stage I nonseminomatous testicular cancers. They found that among 42 patients with relapsed disease, only one of eight patients with disease in the chest had isolated intrathoracic recurrence detected only by CT. They concluded that eliminating chest CT from routine follow-up reduced radiation exposure without compromising the outcome (85). Others have debated this finding and suggest that 5% of recurrences

are detected at CXR alone (86). For restaging of the abdomen, most organizations recommend routine CT follow-up with decreasing frequency over time. Bradford et al. summarize the numerous follow-up options proposed by various medical organizations (81). Individuals with stage 2 disease at initial surgery maintain a high cure rate after adjuvant chemotherapy and most organizations recommend a CT follow-up sequence similar to that used in patients with stage I disease.

PET/CT for Testicular Cancer

Initial diagnosis

There is currently no clear role for PET or PET/CT in the initial diagnosis of testicular cancer. The relatively high metabolic activity observed in the normal testicle might preclude early detection of small primary tumors, and further research in this area would be of interest. However, the financial cost and radiation exposure of PET/CT, combined with the high cure rate of testicular cancer detected by conventional means will likely continue to argue against any role for PET/CT in initial diagnosis unless new instruments or tracers are developed. For now there are only two case reports demonstrating the ability of FDG PET to diagnose testicular cancer. In 2003, Wolf and coworkers reported a case of a 28-year-old male with prior left orchiectomy due to testicular cancer in which FDG PET performed for elevated tumor markers detected a second primary mixed testicular carcinoma in the contralateral testis (87). Similarly, Ali et al. in 2007 reported the incidental detection of a 1.2×0.9 cm seminoma on PET (SUV 3.7) in a patient undergoing staging of colon cancer (88). These early reports suggest that further study might prove interesting.

Initial staging

Once a testicular cancer has been confirmed, typically by inguinal orchiectomy, the patient may require further staging to determine the best treatment options which can include careful observation, abdominopelvic lymph node dissection, chemotherapy or radiation therapy depending on the histological subtype and clinical situation. Metastatic disease is present in 30% of newly diagnosed seminomas (Fig. 20) and in 70% of nonseminomatous tumors (89) and, therefore, accurate staging of testicular cancer is important for the planning of additional therapy.

In a larger 1998 study containing a mixed population of patients at varying stages in the treatment of testicular cancer, Cremerius and coworkers (90) performed FDG PET on 12 patients with newly diagnosed testicular cancer. Readers were aware of CT findings at the time of scan interpretation and validation of findings was performed by

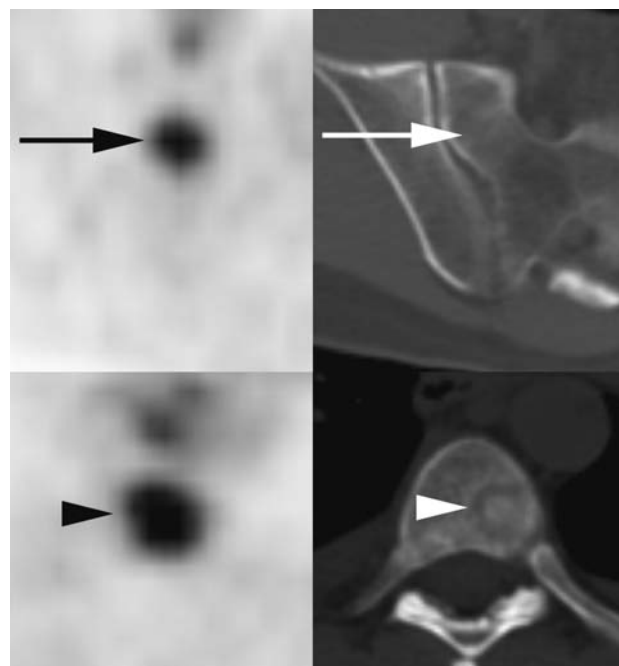


Figure 20 A 49-year-old male with metastatic seminoma. In addition to FDG-avid bone metastases visible on CT (*arrow-heads*), PET/CT reveals additional osseous metastases that are not visible on CT (*arrows*).

clinical follow-up or histology. PET and CT performed equally with a sensitivity of 83% and a specificity of 83% for detection of residual metastatic disease. Seminomas were noted to have higher uptake than other types of testicular cancer. Not surprisingly, PET performed better in these patients.

Also in 1998, Muller-Mattheis and coworkers examined the utility of FDG PET in the initial staging of testicular cancer. In 21 patients with clinical stage I pure seminoma, FDG PET results were identical to findings at computed tomography. In seven patients with nonseminomatous stage I testicular cancer, PET result was false negative in four patients with micrometastases. PET did find metastatic disease in one patient with a negative CT scan and normal tumor markers (91).

In 1999, Albers compared the accuracy of FDG PET and CT for initial staging of 37 patients with clinical stage I (25) and II (12) germ cell tumors. Truth was determined by surgical staging in nonseminomatous cancer and follow-up in seminoma. PET correctly staged 34 of 37 patients compared with 29 of 37 with CT. Seven metastases were detected by PET and four were identified by CT. Of note, PET did not detect any tumor less than 0.5 cm and failed to identify a metastatic 4.8 cm mature teratoma. When looking at various small subgroups, the authors concluded that PET offered no advantage over CT in the initial staging of clinical stage I tumors but was able to identify

additional metastases in patients with clinical stage II disease and thus might potentially be useful for treatment decision making. Ultimately, further study was suggested before changing conventional management (92).

Similarly, Cremerius reported in 1999 on a study of 50 patients with newly diagnosed germ cell tumors (93). PET detected metastatic disease with a sensitivity and specificity of 87% and 94% compared with 73% and 94% for CT and 67% and 100% for tumor markers, respectively. These numbers suggest a possible slight advantage of PET over CT but were not statistically significant. The authors concluded that larger trials were required for a final conclusion.

In 2000, Hain (94) also examined the ability of FDG PET to detect metastatic disease in a population of patients with varying types of testicular cancer (Fig. 21). FDG PET identified metastases in 10 patients and the result was false negative in five patients. Disease stage was increased in several patients who were found to have visceral or bone metastases. They concluded that PET might again be useful but requires further study.

Sperman and colleagues (95) in 2002 examined the utility of FDG PET to stage patients with newly diagnosed nonseminomatous germ cell tumors (NSGCT). In patients with stage I NSGCT, PET staging was equivalent to CT. In stage II NSGCT, PET failed to identify a mature teratoma and a retroperitoneal mass containing a small amount of embryonal carcinoma whereas CT was correct in all cases. The authors concluded that PET offered no advantage over CT in initial staging.

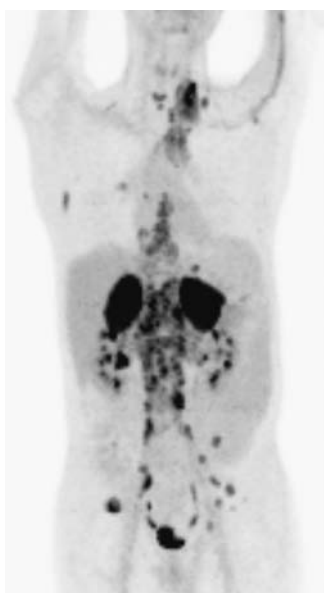


Figure 21 Maximum intensity projection image from PET/CT in another patient with seminoma reveals osseous and lymph node metastases above and below the diaphragm.

In 2002, Tsatalpas and colleagues (96) reported on experience with FDG PET in the initial staging of testicular germ cell tumors. Twenty-one patients were studied and PET reportedly demonstrated higher sensitivity, accuracy, and negative predictive value compared with CT for detection of metastatic infradiaphragmatic and supra-diaphragmatic lesions. Differences between CT and PET were not statistically significant.

In 2003, Lassen (97) reported on the utility of PET at initial staging in patients with NSGCT who had a negative CT scan and normal tumor markers. In 46 patients studied, 10 patients developed recurrent disease and 7 of the 10 had a positive PET result at initial staging. This suggests that PET may offer an advantage over CT in the initial staging of NSGCT.

In conclusion, current evidence demonstrates no clear advantage of PET over CT in the initial staging of patients with germ cell tumors. A few reports raise the possibility of a slight advantage with PET for detection of metastases whereas several studies suggest no definite benefit. Further studies are required. No studies to date have compared PET/CT with PET or a combination of PET and separately acquired diagnostic CT. In theory, a PET/CT scan may lead to improved specificity and, in some cases perhaps, improved sensitivity for detection of low-grade metastases as is seen in some patients with tumors containing a high volume of teratoma. Newer PET detector rings employed in the latest cameras may also impart a potential advantage not seen in the initial studies.

Restaging after therapy: nonseminoma germ cell tumors

Current studies of the efficacy of PET in the restaging of nonseminoma germ cell tumors have focused on characterizing residual soft tissue mass in patients who initially presented with stage II or III disease. There are few studies examining the ability of PET or PET/CT to detect early recurrence in patients who initially presented with stage I disease (Fig. 22). In 2003, Lassen reported on the utility of PET to detect residual cancer in patients with negative CT and tumor marker values after treatment. The main challenge during the restaging of nonseminoma germ cell tumors is to characterize residual tumor mass, which can either be nonviable or contain teratoma or residual carcinoma. In 1996, Stephens examined 30 patients with residual tumor mass using PET and found a median SUV of 2.9, 3.1 and 8.8 for necrosis/fibrosis, teratoma or viable germ cell tumor (98). These findings suggested that PET can identify viable germ cell tumor but cannot differentiate teratoma from necrosis and fibrosis. The risk of malignant degeneration of teratoma and need for surgical resection thus limited the value of PET. Nuutinen (99) also examined a similar population and found that three out of nine positive PET scans were due to inflammation and not tumor, further questioning the

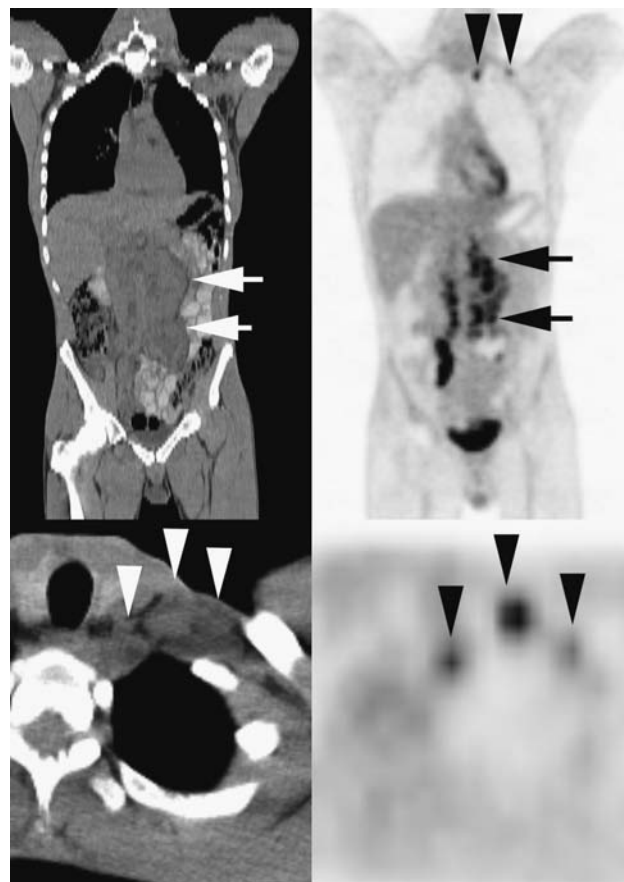


Figure 22 A 28-year-old male status postorchietomy one year ago because of nonseminomatous germ cell tumor. The patient presented with elevated tumor markers. FDG PET/CT revealed recurrent disease in the retroperitoneum (arrows) with extensive lymphadenopathy on PET and CT. PET images revealed occult metastases in the left supraclavicular region within subcentimeter lymph nodes that are difficult to visualize on CT (arrowheads), increasing the stage of the disease from II to III.

value of PET for characterizing residual mass. In 2002, Sanchez and coworkers reported on the accuracy of FDG PET in the classification of residual mass or suspected recurrence following chemotherapy for a mixed group of patients with nonseminomatous testicular cancer. Twenty-five scans were performed in 15 patients. PET detected retroperitoneal disease before CT in three patients. The PET result was false negative in two patients with CT pathology who were found to have residual mature teratomas at surgery (100). Although, this study hints at utility, but it was too small and limited to draw definitive conclusions about the use of PET in NSGCT.

Kollmannsberger (101) examined a larger population of 45 patients with residual tumor mass after chemotherapy and found a sensitivity of 59%, specificity of 92%, a positive predictive value of 91% and a negative predictive

value of 62% for characterization of residual tumor. CT performed with a sensitivity of 59% and a specificity of 92%. The authors concluded that PET offered additional value. However the low sensitivity calls in to question the usefulness of a negative scan.

Restaging after therapy: pure seminoma

As is the case in nonseminomas, the PET literature for follow-up has focused on characterization of residual disease seen on CT (Fig. 23). In 1999, Ganjoo and coworkers (102) initially examined the utility of PET in restaging patients with residual tumor mass on CT following chemotherapy (Fig. 24). They found that PET offered no additional value because of the fact that the majority of the lesions were nonviable and stable during follow-up. Although interesting, this study did not contain sufficient patients with residual viable tumor to assess the true value of PET. In 2001, De Santis (103) provided more encouraging data in a review of 37 PET scans in patients with seminoma and bulky residual disease. They found a sensitivity of 89% and a specificity of 100% for characterization of residual seminoma within residual mass. All lesions greater than 3 cm were correctly characterized and 22 of 23 lesions less than 3 cm were also correctly characterized.

Several preliminary studies that contained germ cell tumors of various histological subtypes looked separately at the data for seminomas with no other histological component. Spermon and coworkers (95) in 2002 reported that PET correctly restaged 9 of 10 patients after chemotherapy for metastatic disease. Only one patient had viable tumor, and therefore definitive conclusions could not be made from this paper.

In 2005, Becherer reported on the performance of PET for detection of residual viable tumor in 54 patients with a

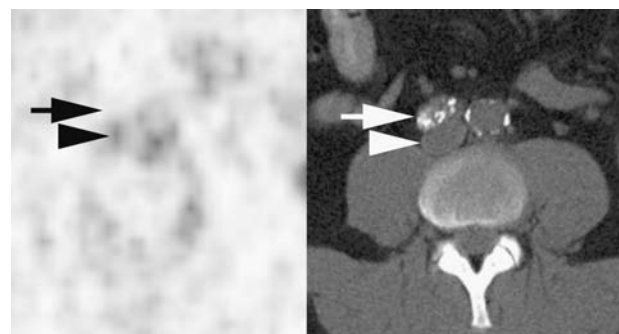


Figure 23 A 55-year-old male with a history of seminoma treated with surgery and chemotherapy. CT at completion of therapy revealed a residual retroperitoneal mass that was not metabolically active on PET/CT (arrows). The mass was correctly classified as nonviable on PET/CT and remained stable for two years. Note adjacent physiological vascular activity (arrowheads) that was properly classified on the basis of PET/CT fusion.

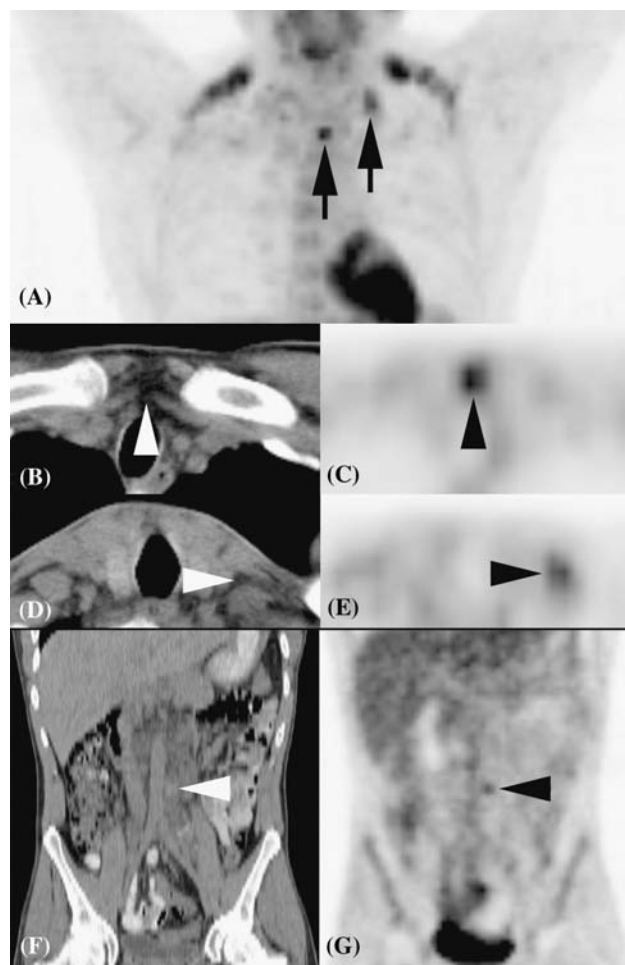


Figure 24 Advantage of PET/CT. Same patient from Figure 21 following chemotherapy. (A) Prior active supraclavicular nodes have completely responded to therapy and new foci on PET have appeared (arrows). (B–E) PET/CT demonstrates with a high degree of certainty that new foci (arrowheads) correspond to brown fat and not tumor. (F–G) Retroperitoneal lymphadenopathy has markedly decreased in size on CT. (F) PET from PET/CT demonstrates a tiny focus of residual viable tumor (arrowheads). (G) CT alone would not be able to determine tumor viability within the residual lymphadenopathy.

history of pure seminoma and who were treated with chemotherapy. Seventy-four residual masses were detected at CT. PET detected viable tumor with a sensitivity of 80% and a specificity of 100% compared with CT which demonstrated a sensitivity of 73% and a specificity of 73% when using a threshold of 3 cm for determination of residual tumor. Of note, PET was 100% sensitive for all residual tumors measuring greater than 3 cm. The authors concluded that a negative PET result ruled out viability, helped prevent unnecessary surgery for all larger lesions, and was highly specific when positive in smaller lesions (104).

In 2006, Lewis (105) reported on a similar retrospective study of patients with pure seminoma and residuals soft tissue masses following chemotherapy. In 24 PET scans they found a sensitivity of 100% for detection of residual disease. However, there were two patients with lesions greater than 3 cm that were false positive and two of three positive studies in lesions less than 3 cm were false positive. The authors concluded that a negative scan was highly reassuring and could be used to select observation over surgery. A positive study must however be interpreted with caution because of the frequency of false positives.

Prognosis and treatment response

Assessment of treatment response could have a potential role in the direction of appropriate chemotherapy. In 1995, Wilson and coworkers (106) performed FDG PET on patients with stage II–IV testicular germ cell tumors. In three patients, reductions in FDG uptake were observed after chemotherapy and were predictive of overall treatment response. Two patients showed no decrease in FDG uptake with chemotherapy and were ultimately determined to be nonresponders. In 2002, Bokemeyer examined the ability of FDG PET to predict treatment response in 23 patients with relapsed metastatic germ cell tumors. Patients underwent induction chemotherapy followed by FDG PET, CT and measurement of tumor markers prior to a high-dose chemotherapy regimen. PET accurately predicted subsequent response to high-dose chemotherapy in 91% of patients compared with 59% for CT and 48% for tumor markers. Of note, eight patients with a favorably predicted outcome by CT and tumor marker measurement had a positive PET scan and progressed. The authors conclude the PET may be useful to select patients who will benefit from high-dose chemotherapy (107). A follow-up study (108) from the same group in 2004 found that tumor markers performed better with PET, CT and markers correctly predicting response to high-dose chemotherapy in 89%, 67%, and 88% of patients, respectively. In conclusion, there is preliminary data suggesting that metabolic response assessment with FDG PET may be useful for determining prognosis and predicting which patients will benefit from high-dose chemotherapy and who will not. Further studies are required before PET or PET/CT becomes a standard tool for predicting response in relapsed disease.

Other tracers

Little work has been done to investigate other tracers for PET imaging of testicular cancer. Kole and coworkers (109) examined the use of ^{11}C -tyrosine in patients with known retroperitoneal metastases of nonseminoma testicular germ cell tumors. Only 20% of known metastases were visualized and the authors concluded that radiolabeled tyrosine was not useful.

Non-germ cell tumors

Nongerm cell tumors of the testicle include Leydig cell tumors, Sertoli cell tumors and gonadoblastomas. The majority of these are benign, and there has been no systematic investigation of the use of PET for these tumors. There is one case report of PET detection of a sertoli cell tumor in a patient undergoing imaging of a right lung cancer (110).

Testicular metastasis and testicular lymphoma

There are few studies examining the role of PET or PET/CT in the identification of testicular metastases or testicular lymphoma. To date, two case reports describe detection of relapsed non-Hodgkin's lymphoma in the testicle on FDG PET (111,112). Others have reported PET detection of testicular metastases from melanoma (113).

Summary of PET and PET/CT in Testicular Cancer

PET and PET/CT currently have no clearly defined role in the diagnosis of testicular cancer. For initial staging, CT and FDG PET appear to perform at similar levels. Further studies with PET/CT may be useful in determining if there is an advantage over CT alone. FDG PET and PET/CT are most useful in characterizing large residual masses following therapy for metastatic testicular cancer and may play a role in monitoring of treatment response.

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Detecting and Evaluating Osseous Metastases on PET/CT

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DETECTING AND EVALUATING OSSEOUS METASTASES ON PET/CT

Accurate localization and assessment of the extent of metastatic bone disease is essential for the selection of optimal therapy. Surgical treatment or radiation therapy may be employed in localized metastatic lesions associated with pain or fracture. Widespread bony metastatic disease requires either systemic chemotherapy or hormonal therapy with or without the addition of external beam radiation or radioisotope therapy for bone pain (1–3). Furthermore, as the new therapies with biphosphonates have improved the survival of patients with bone metastases (4), quantitative analysis and follow-up of therapeutic response gain even greater importance. While in the past bone scintigraphy using Technetium-99m (Tc-99m) labeled diphosphonates has been the standard for detecting and following bone metastases, total-body magnetic resonance imaging (MRI) has shown significant promise (5). In addition to detection of bone metastases, fluorodeoxyglucose (FDG) or sodium fluoride (NaF) positron emission tomography

(PET) offers metabolic information including assessment of tumor viability and activity. When combined with computed tomography (CT) and used in the context of integrated PET/CT, PET provides additional anatomic information such as precise localization of bony involvement, associated fracture risk, or in the spine, cord, or nerve impingement: 5% of vertebral metastases lead to vertebral body compression; 10% may be associated with soft tissue involvement around the spine. The incremental diagnostic value of integrated PET/CT in oncology has been reported to be as high as 60% on a per-patient basis and 55% in a region-based analysis of breast cancer (6), but lower percentages 18% to 22% have been reported in other solid tumors (7,8). This is largely due to the increased accuracy of PET/CT (98% vs. 83%) (9) as it helps to differentiate benign from malignant lesions, gives the precise anatomic mapping of the lesion, e.g., the level of the spine involved; and in the chest, in-line PET/CT, correctly distinguishes among pleura, rib, liver, lung, or chest wall. Also, significant numbers of incidental CT findings are identified in a small percentage of patients,

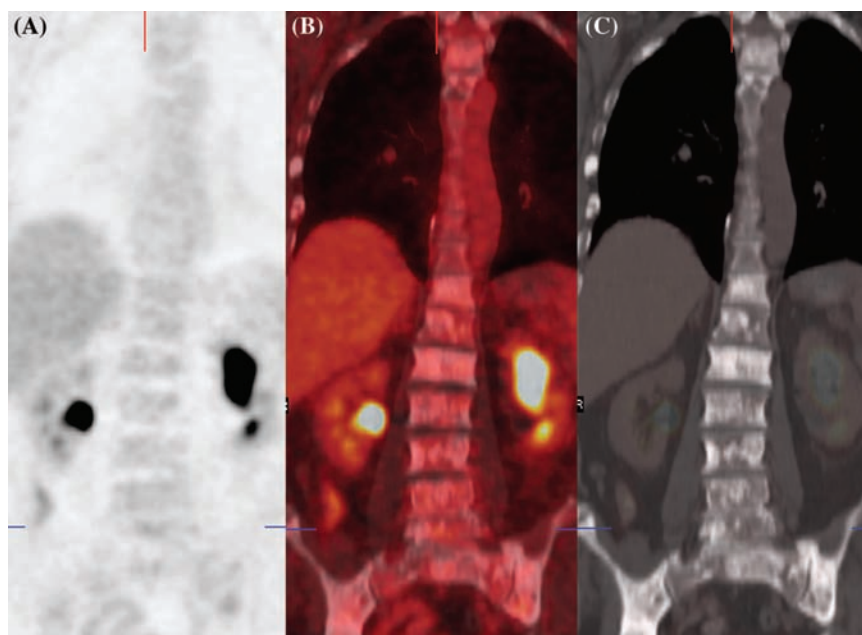


Figure 1 A 72-year-old man with metastatic prostate cancer. (A) Coronal FDG PET and (B) fused shows no increased uptake in the spine in spite of obvious sclerotic metastases in the vertebral bodies on (C) coronal CT.

in one series 3% (7 of 250) who underwent PET/CT (10). In the setting of metastatic bone disease, in particular, CT may show sclerotic bone metastases, inactive on the FDG PET portion of the study (Fig. 1).

Both NaF and FDG have been employed to assess bony metastases and both are FDA approved. While NaF PET offers exquisite sensitivity, it lacks specificity just as radiolabeled diphosphonates do (11). Recent data (11–13) suggest that NaF PET/CT has a higher specificity compared with Na¹⁸F PET alone, again because of the anatomic and morphologic information added by the CT, and further studies are required to assess its role in comparison with FDG PET/CT.

PET RADIOTRACERS FOR BONE METASTASES

Other fluorinated (F-) tracers alternative to FDG are now being investigated in PET imaging, even if their role in cancer detection is not well settled as yet (14–18) (Table 1). Fluorinated aminoacids analogues reflect the increased transport and/or protein synthesis, typical of tumor cell. These tracers appear to be more specific for tumors than FDG. Fluorine-octreotide analogue has been employed particularly in neuroendocrine tumors, but also in brain, medullary thyroid cancer, small cell lung cancer, and lymphomas. A better target/background has been described for octreotide analogues conjugated with

Table 1 Fluorinated Tracers Alternative to FDG

Fluorinated (F-) aminoacids analogues	2-[¹⁸ F]fluoro-L-tyrosine (F-TYR) L-3-[¹⁸ F]fluoro- α -methyl tyrosine (FMT) <i>O</i> -(2 [¹⁸ F]fluoroethyl)-L-tyrosine (FET) 6-[¹⁸ F]-DOPA (FDOPA)
Fluorine-octreotide analogues	(<i>N</i> (α)-(1-deoxy-D-fructosyl)- <i>N</i> (ϵ)-(2-[¹⁸ F]fluoropropionyl)- Lys(0)-Tyr(3)-octreotide ([¹⁸ F]FP-Gluc-TOCA)
Fluorine-nucleosides	3'-deoxy-3'-[¹⁸ F]-fluorothymidine (FLT) ¹⁸ F-FBAU(1-(2-deoxy-2-fluoro-1- α -D-arabinofuranosyl)-5-bromouracil) ¹⁸ F-FMAU(2'-fluoro-5-methyldeoxyuracil- β -D arabinofuranosyl) ¹⁸ F-FAU(2'-fluorodeoxyuracil- β -D-arabinofuranosyl)
Fluorine-analogues of membrane phospholipids	[¹⁸ F]fluoromethylcholine (FCH)
Fluorine-estrogen-related analogues	16 α -[¹⁸ F]fluoroestradiol-17 β ([¹⁸ F]FES)
Fluorinated hypoxia tracers	[¹⁸ F]fluoromisonidazole (F-MISO)

carbohydrates. Fluorine-nucleosides are incorporated into the DNA, showing a low sensitivity in the liver and bone marrow. Fluorine-analogues of membrane phospholipids are trapped in malignant cells as they develop an enhanced activity of the choline kinase. Several fluorine estrogen-related analogues have been investigated, but to date the only one that has been clinically evaluated is 16α -[^{18}F] fluoroestradiol- 17β ([^{18}F]FES). This analogue has been used primarily in breast cancer and in the setting of hormonal therapy. Fluorinated hypoxia tracer uptake, even with a threshold, gives a good estimate of tissue hypoxia. This evaluation is expected to allow better radiation-therapy planning in the future by dose adjustment to relatively hypoxic regions or incorporation of other manipulations that might improve oxygenation.

Other fluorinated tracers are under evaluation, e.g., 5-[^{18}F]-fluorouracil (5-[^{18}F] FU) and tracers for gene expressions, but they are not yet generally available.

Clinically, [^{18}F] FDG PET/CT is used more widely than any of the others for oncologic diagnosis and, thus, will provide an assessment of osseous metastases at the same time.

FDG PET AND PET/CT FOR IDENTIFYING BONE METASTASES

Strict criteria for positivity on FDG PET do not exist, but certainly focally increased uptake above background level of marrow activity identifies a lesion. This criterion, combined with clear-cut lytic, sclerotic, or mixed CT abnormalities, increases our confidence. (Fig. 2). The typical CT appearance of blastic, sclerotic lesions are dense areas, but somewhat less dense than the cortex, and show loss of the usual trabecular pattern. These lesions have no clear delimitation from the normal bone. Periosteal reaction may be a feature (Fig. 3). In the spine, paravertebral masses and cortical involvement are rare with sclerotic lesions.

Sometimes focal FDG uptake will fuse to a normal-appearing bone, and small lytic lesions may not be seen on CT. Where fatty marrow normally occurs, there may be only subtle changes in density from fat to soft tissue density. When visible on CT, lytic lesions are characterized by the soft tissue replacement of the bony trabeculae and can be associated with bone necrosis or calcifications. Cortical destruction is highly specific for a malignant lesion (Fig. 4). At the earlier stages of cortical encroachment, only endosteal erosion of the cortex may be evident. In the spine, pedicular destruction, epidural encroachment, or paravertebral masses may be seen (19).

Much has been written about the relative roles of FDG PET and Tc-99m diphosphonate bone scanning in the

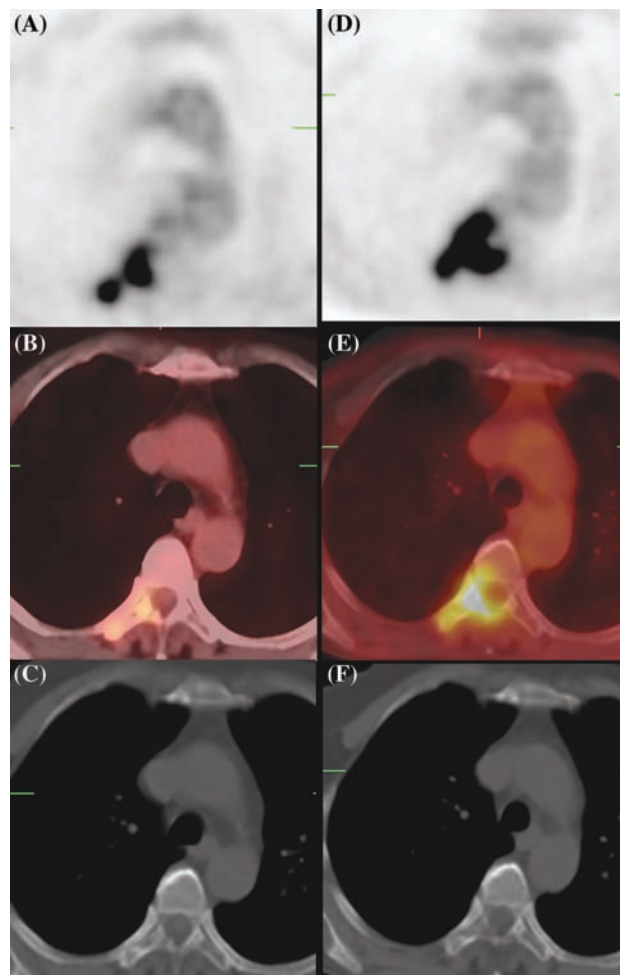


Figure 2 A 59-year-old man with lung cancer. Axial view of metastasis of the right pedicle and rib: on the left column, (A) FDG-PET, (B) fused PET/CT, and (C) CT images at baseline. (D–F) Progression is shown three months later on the right column. Noteworthy is that the area of uptake in the lesion became more extensive on PET, while remaining relatively unchanged on CT.

detection of bone metastases. Still controversial is whether the use of FDG PET can obviate the need to perform a separate bone scan. This controversy has been extensively discussed in lung carcinoma (20,21). Because bone scintigraphy includes the whole body in most patients, and because of its availability, low cost, and high sensitivity (5), conventional bone scan is still considered the most cost-effective tool, but the complementary role of these two techniques has been suggested (22–24). Furthermore, the addition of CT to either modality single-photon emission computed tomography (SPECT/CT or PET/CT) in order to correctly locate and characterize bone lesions is invaluable. Overall, a PET/CT examination will obviate the need in general for a separate CT for bone lesions clearly identified also on the CT images of

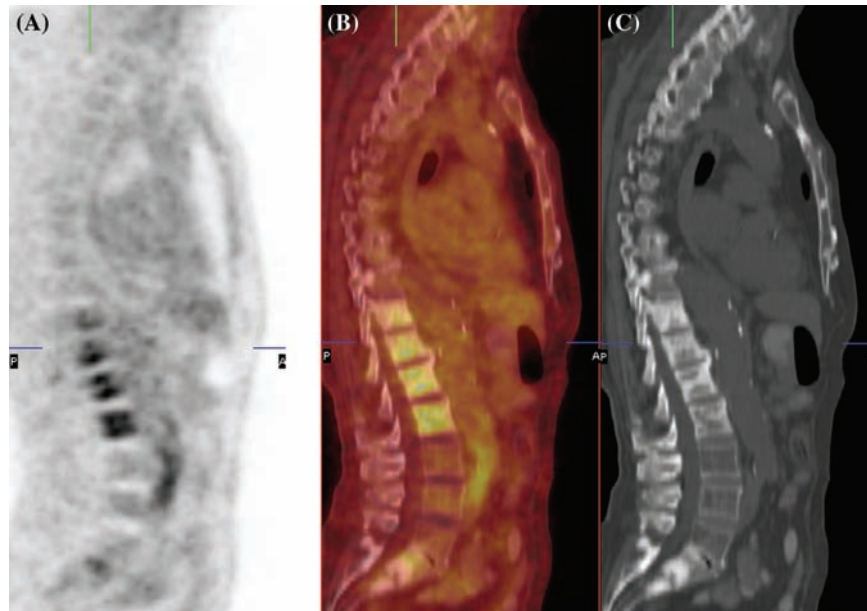


Figure 3 Sagittal view of FDG-avid bone metastases of the spine from prostate cancer (T11, T12, L1, L2, and S1): (A) FDG-PET, (B) fused PET/CT, and (C) CT images. Note the absence of defined trabeculae within the sclerotic metastasis. This patient had a history of prostate cancer, which is not always metabolically active on FDG PET.

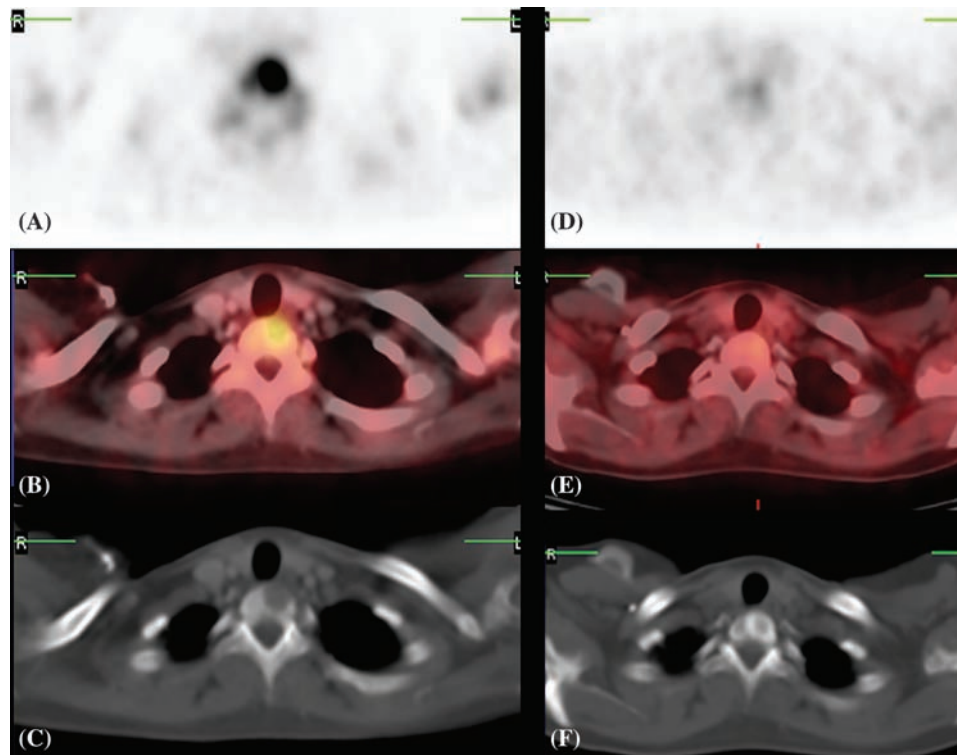


Figure 4 Lytic metastasis of T1 in a patient with metastatic breast cancer. To the left, the anterior aspect of T1 is (A) FDG-avid and (B) fuses to a lytic lesion on (C) CT; to the right, the same lesion after radiation therapy is less active on (D) PET and (E) fuses to the metastasis that now has a sclerotic margin on (F) CT.

Table 2 Overview of Reported Sensitivity and Specificity for FDG PET in Bone Metastases Detection—Primary Bone Tumors Not Included

Author (Ref.)	Year	No. pts. (Type of cancer.)	Modalities compared	Sens %	Spec %	Comments
Ohta (35)	2001	51 (breast)	FDG PET/BS	77.7	97.6	
Uematsu (66)	2005	15 (breast)	FDG PET/BS	17	100	
Abe (36)	2005	44 (breast)	FDG PET/BS	84	99	Lesion based
Yang (37)	2002	40 (breast)	FDG PET/BS	95.2	90.9	
Gallowitsch (28)	2003	62 (breast)	FDG PET/CI	97.1	82.1	
			FDG PET/BS	56.5	88.9	Lesion based
			FDG PET/BS	92.3	92	Patient based
Nakai (31)	2005	55 (breast with bone mets)	FDG PET/BS	80	88.2	
Dose (67)	2002	50 (breast)	FDG PET/BS	83.3	89.4	
Metser (30)	2004	51 (spine mets)	PET/CT	96	56	Lesion based
				98	50	Patient based
Nakamoto (26)	2005	55 (multiple primaries)	FDG PET/CT	74.3	—	
Israel (29)	2006	131 (multiple primaries)	FDG PET/CT	59	—	Lesion based
Liu (38)	2006	30 (NPC)	FDG PET/BS	70	98.8	
Sugiyama (68)	2004	19 (HCC)	FDG PET/BS	80		
Goerres (69)	2005	34 (oral cavity)	FDG PET/CT	100	91	
Daldrup-Link (70)	2001	39 children (multiple primaries)	FDG PET/BS/ WB MRI	90	—	Lesion based
				85.7	88.9	Patient based
Dimitrakopoulou-Strauss (71)	2002	83 (benign vs. malignant lesions)	Dynamic FDG PET	54	91.3	
Najjar (72)	2001	36 (low-grade NHL)	FDG PET/ CT/physical examination	87	100	Lesion based
Pakos (73)	2005	587 (lymphoma)	FDG PET/ BMbx	51	91	(Meta-analysis)
Fuster (74)	2006	106 (lymphoma)	FDG PET/ BMbx	86	99	
Yeh (49)	1996	13 (prostate)	FDG PET/BS	18	—	
Shreve (48)	1996	22 (prostate)	FDG PET	65	—	
Morris (44)	2002	17 (prostate)	FDG PET/BS	76.7	—	
Schöder (75)	2005	91 (prostate)	PET/CI	31	—	
Bury (21)	1998	110 (NSCLC)	FDG PET/BS	90	98	
Marom (20)	1999	100 (lung)	FDG PET/BS	92	99	
Gayed (76)	2003	85 (lung)	FDG PET/CI	73	88	
Cheran (77)	2004	257 (lung)	FDG PET/BS	91	96	

Abbreviations: Sens, sensitivity; Spec, specificity; BS, bone scan; CI, conventional imaging; NPC, nonkeratinizing nasopharyngeal carcinoma; BMbx, bone marrow biopsy; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; WB MRI, whole-body magnetic resonance imaging; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease.

the PET/CT even given the compromised quality of the low dose images. Table 2 is an overview of the literature reporting sensitivity and specificity of FDG PET in detecting bone metastases.

FACTORS DETERMINING FDG UPTAKE IN METASTASES

The performance of FDG PET, based on the level of FDG uptake in bone lesions likely reflecting the proliferative activity of those lesions, depends on the pathophysiologic mechanisms of metastases.

Stage of Development of Metastases

Intramedullary metastases occur in the early phase of bone involvement by means of hematogenous spread to red active marrow. These lesions are seen as FDG avid and MRI positive (25) when large enough to be resolved by PET, while bone scan and CT may remain negative (5,26). As the metastatic lesion enlarges within the marrow, the normal remodeling balance between osteoclastic (bone resorption) and osteoblastic (bone formation) activity is impaired, and one pattern usually prevails over the other. Therefore, bone metastases across different types of primaries are classified on the basis of X-ray and CT

Table 3 Patterns of Bone Metastases According to Primary

Lytic	Sclerotic/blastic and mixed
Almost all tumor types	prostate
Bladder	stomach
Kidney	pancreas
Thyroid	uterus (adenocarcinoma)
Lung (squamous-cell and oat-cell carcinomas)	lung (Adenocarcinoma and bronchial carcinoid)
Breast	breast
Uterus (cervix)	nasopharyngeal carcinoma
Ovary	retinoblastoma
GI tract (stomach, colon)	osteogenic sarcoma
melanoma	treated/healing metastases
Nasopharyngeal carcinoma	
Neuroblastoma	
Ewing's sarcoma	
Medulloblastoma	
Multiple myeloma	
Leukemia	

Source: From Refs. 19, 27, 78.

appearance as lytic (approximately 50%), sclerotic (or blastic, approximately 35%), and mixed (approximately 15%) (Table 3) (5,27). Significant differences have been shown by several authors in the performance of FDG PET in detecting bone metastases according to their morphologic pattern (Table 4). In particular, lytic metastases more than sclerotic ones appear to display a greater FDG avidity (26,28–31), probably because of a higher glycolytic rate and hypoxia (32) (Fig. 1). Also, low FDG uptake of sclerotic lesions may be related to a small volume of malignant cells (33).

In patients with breast and lung primary tumors, an important issue still to be resolved is whether FDG PET negative, bone scan positive (or indeed CT positive) lesions are clinically relevant (34), since sclerosis may also be due to healing after treatment (29) (Fig. 5).

Anatomic Location

The spine is the most common site of metastatic spread, followed by the ribs. Several authors have compared FDG PET with planar bone scanning (31,35–38) and/or conventional imaging tools. FDG PET seems to be more reliable for lesions in the spine and pelvis, where bone scan lacks sensitivity; while bone scan has a better accuracy in the remainder of the skeleton.

SPECT using Tc-99m-labeled diphosphonates (39–42) and the hybrid system SPECT/CT (43) improve sensitivity of bone scintigraphy because of better detection of the posterior elements of the spine, but a better specificity for metastatic involvement in the body of the vertebra has yet to be proved. Also, for the time being, routine use of SPECT with most equipment, requiring multiple separate tomographic acquisitions to assess the entire skeleton, is impractical. Also, most FDG PET scanning protocols employed in solid cancers do not often include the lower legs and the skull. While the first are rarely sites of bony metastases, especially early in the course of skeletal involvement, the latter may be. Sensitivity for skull metastases may be compromised by the high FDG uptake of the adjacent brain.

Several tumors are known to be relatively non-FDG avid, but when these tumors become more aggressive

Table 4 Sensitivity of FDG PET According to CT appearance of Bone of Metastases

Author (Ref.)	Year	No. pts. (Type of cancer)	Sensitivity %		
			Lytic	Sclerotic	mixed
Metser (27)	2004	51 (multiple primaries)	100	88	100
Nakai (28)	2005	55 (breast)	100	55.6	94.7
Abe (33)	2005	44 (breast)	92	74	—
Israel (26)	2006	131 (57 solid tumors, 19 lymphomas)	79.5	38.6	—

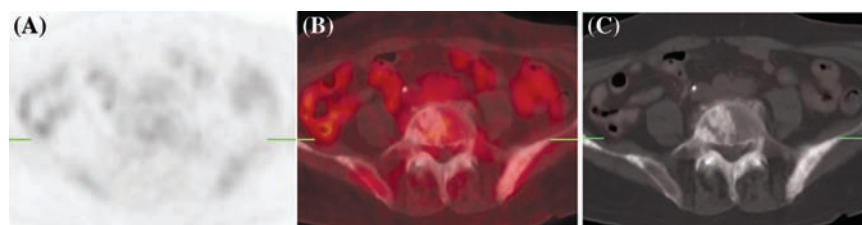


Figure 5 A 71-year-old woman with bony metastases secondary to breast cancer. After chemotherapy, no activity on (A) PET is seen (B) fusing to sclerotic lesions in the spine and pelvis on (C) CT are seen. Her tumor markers at this time were within normal range.

showing distant metastases and/or progression, they are more likely to show FDG uptake. In tumors usually classified as low grade, e.g., prostate or differentiated thyroid carcinoma, progressive lesions tend to show FDG uptake (Fig. 3) (34). Available studies do not necessarily focus on bone metastases alone in some of these tumors, but one could potentially infer from the experience in extraosseous metastases (44,45).

Previous Treatment

As seen in clinical practice, FDG uptake of bone metastases can be influenced by anticancer treatment (chemo and/or radiation therapy). The most accurate method for measuring FDG uptake has not been established yet (46). Several studies have been published, mainly focusing on breast (17,47) and prostate (44,48,49). These studies all show a strong correlation between changes in FDG uptake in bone metastases in relation to treatment and tumor response or lack thereof (Fig. 2). Recently, Israel and coworkers (29) analyzed 131 patients with bone metastases from several types of cancers (57 solid and 19 lymphoma) to assess FDG and CT pattern changes after treatment. After treatment, incongruent CT-positive/PET-negative lesions were more prevalent, mostly with a sclerotic appearance, presumably reflecting healing as a direct effect of treatment. On the other hand, most untreated lesions were PET positive and had a lytic appearance on CT (Fig. 4).

Also, metabolic response on FDG PET after cancer treatment in metastatic patients may represent a potentially positive prognostic factor. Its value for predicting long-term survival has not yet been evaluated (50,51). While a “flare phenomenon,” defined as an increase in the number or intensity of bone lesions with subsequent improvement while the patient is receiving chemotherapy, is widely reported in conventional bone scans, relatively sparse literature exists on this issue and that of PET (17,52,53). However, in patients treated with hormonal therapy for breast cancer, stable or increasing FDG uptake has been seen 7 to 10 days after institution of therapy. Of interest in those patients treated with hormones in that study was a concomitant decrease in the uptake of [^{18}F]FES in metastases, which predicted their tumor response. Bone metastases alone did not exhibit this behavior. Wade (53) reported a single case of an osseous flare response in the thoracic spine seen in breast cancer both on bone scan and Na^{18}F -fluoride PET, presumably representing a phenomenon similar to that recognized in bone scintigraphy. In that patient FDG PET showed a decrease in activity. Clearly, this issue requires further study, and the wider use of PET/CT with these various radiotracers can potentially contribute to a better definition of metabolic “flare” response to therapy and help define the best means for assessing therapeutic response.

FALSE-NEGATIVE FDG PET/CT

Only a few studies have evaluated for FDG the phenomenon of “stunning,” defined as a low uptake in lesions of patients undergoing or having recently undergone chemotherapy. This phenomenon may occur through a direct effect on the expression of GLUT1 receptors and Hexokinase II (54). Jacene et al. (55) evaluated in vitro ^3H -FDG uptake both in untreated conditions and during treatment with either doxorubicin or 5-fluorouracil at six time points up to three days. They showed that ^3H -FDG uptake accumulates less in treated cells than in untreated ones and can decline to a greater extent than the number of viable cells. While the possibility of stunning in vivo has been suggested, clinical studies are necessary to further evaluate this phenomenon.

When evaluating the osseous structures, medication with colony stimulating factors (CSFs) should be taken into account. In fact, CSFs are known to increase FDG uptake in bone marrow and spleen through the activation of both progenitor and mature hematopoietic cells. On the one hand, increased diffuse FDG uptake may be identified easily as reactive to recent treatment with CSFs (Fig. 6), but this increased marrow accumulation lowers the sensitivity of FDG for bone lesions. As the effect wears off, a minor amount of heterogeneous normal bone marrow activity can resemble metastases to the bone or bone marrow or obscure a metastasis (56). A period varying between 5 and 30 days between the last CSF-administration and the FDG PET scan may be adequate (56–58). Recently, Jacene and colleagues (55) hypothesized a decreased bio-availability of FDG to extraosseous tumor when bone marrow uptake is increased, raising the possibility that a CSF-stimulated FDG uptake in bone marrow may lower PET scan sensitivity for viable cancer in a sort of “steal” phenomenon.

FALSE-POSITIVE FDG PET/CT

As previously reported (59), FDG is not a tumor-specific radiopharmaceutical, and healthy tissue or benign disease, such as inflammation or posttraumatic repair, can pick up as well. False-positive lesions on PET alone have been reported because of muscle uptake, brown fat, inflammation, blood-pool activity in the great vessels, and bowel uptake. PET/CT allows correct anatomical mapping of these foci of uptake, but still in the evaluation of osseous structures several lesions may be misinterpreted as bony metastases, because of intense FDG uptake or CT appearance, e.g., benign bone tumors, including histiocytic or giant cell-containing lesions (osteoblastoma, brown tumor, aneurysmal bone cyst, sarcoidosis—see chap. 14, “PET/CT Findings in Primary Bone Tumors”), bone

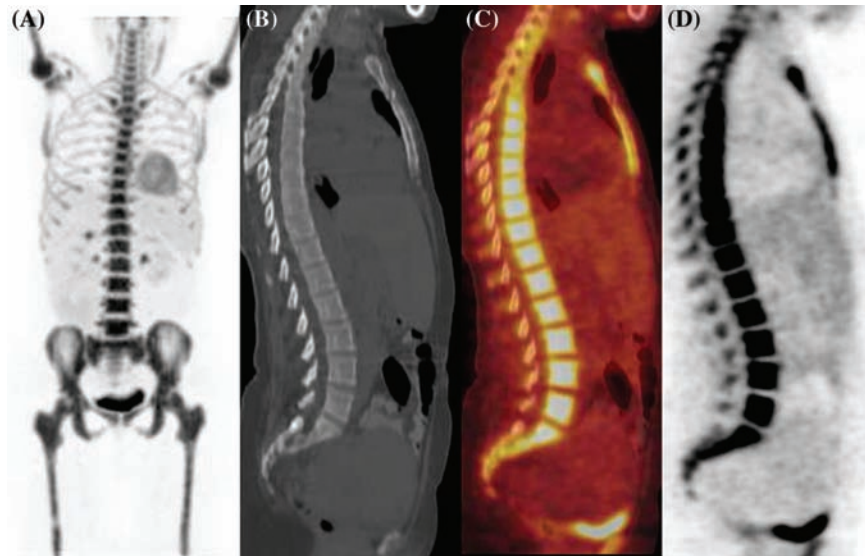


Figure 6 A 44-year-old man with pancreatic cancer on bone marrow support with G-CSF for chemotherapy induced neutropenia. (A) Anterior view of a maximum intensity projection shows diffuse and intense uptake throughout the skeleton and relatively decreased uptake in the organs that usually show activity, e.g., liver, an example of a “steal” phenomenon. In addition, this diffuse skeletal activity has the potential to obscure any potential malignant marrow or bone activity. (B) Sagittal CT scan with bone windows shows normal appearing vertebral bodies. Corresponding (C) fused PET/CT and (D) FDG PET show the intense uptake representing metabolic activity in stimulated hematopoietic cells of marrow.

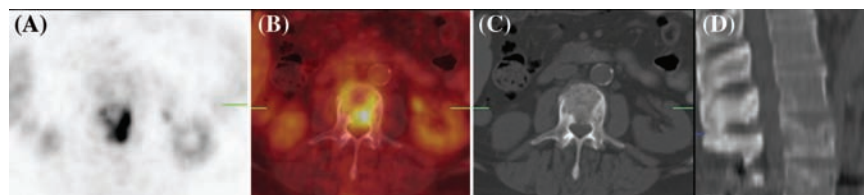


Figure 7 This patient with prostate carcinoma presented to his oncologist with a complaint of back pain. (A) Transaxial PET images of an FDG-avid focus in the lumbar spine, (B) fused PET-CT and (C) CT axial images of the same lesion. (D) Sagittal image clearly shows the wedge deformity of the vertebral body on CT corresponding to the increased uptake. Note that other sclerotic foci on CT are not FDG-avid and that activity fuses to the nonsclerotic aspect of the vertebral body where the fracture is.

islands (vs. small sclerotic bony metastases that are not FDG avid), and fractures (Fig. 7) (60,61). With PET/CT, however, callus or the actual fracture may be apparent on CT. In addition, Schmorl's nodes, usually distinguished by a well-defined radiolucency with a sclerotic margin in continuity with the vertebral endplate on CT, may display FDG activity (Fig. 8). While these are usually easily characterized on CT, an MRI may occasionally be helpful to define a bone defect in the vertebral endplate without signal-intensity alterations.

Of course, occasionally, the attenuation correction based on the CT portion of a PET/CT can cause artifactually increased FDG uptake, caused by beam-hardening due to the presence of too-dense contrast media or with

metal objects (orthopedic prostheses or pacemakers). Examination of the CT and nonattenuated PET images should lead to the correct interpretation of these as artifacts.

FUTURE APPLICATIONS

With the increasing availability of in-line PET/CT, diagnosis, staging, and restaging of several types of cancer is being modified. In spite of improving specificity, in many cases a histological confirmation is required. The combined anatomic/metabolic information given by PET/CT can help in better defining the biopsy target (62). Only one paper has compared the accuracy of PET with that of bone

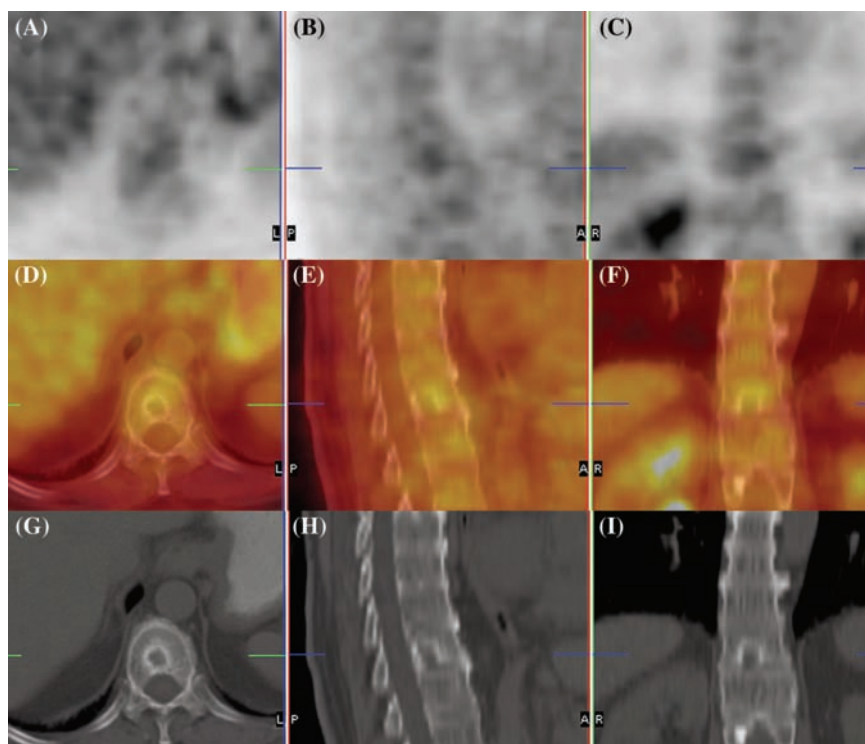


Figure 8 PET axial, (B) sagittal, and (C) coronal images, (D) PET/CT fused axial, (E) sagittal, and (F) coronal and (G) CT axial, (H) sagittal and (I) coronal images of a Schmorl's node, mild to moderately FDG-avid, located on the lower surface of a thoracic vertebral body, in continuity with the disc space, and well margined on CT.

scan in directing skeletal biopsies where no advantage was found for one modality over the other in identifying biopsy sites (63). The retrospective approach of that work might represent a bias. Future applications of clinical PET/CT might also include the incorporation of PET/CT into radiation therapy planning for treatment of isolated or symptomatic bone metastases, a practice currently reserved to head and neck, cervical, and lung cancers (64,65).

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PET/CT Findings in Primary Bone Tumors

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PET/CT FINDINGS IN PRIMARY BONE TUMORS

Limited literature exists concerning the application of flurodeoxyglucose positron emission tomography (FDG PET) or even other radiotracers to the diagnosis, staging, or monitoring of malignant primary bone tumors. However, neuroendocrine tumors and Ewing's sarcoma have received a fair amount of attention. Understandably, the most extensive literature exists in the application of PET to osseous metastatic disease since the patients with known primaries are the ones in which FDG PET is used most extensively. Clinical experience now tells us that FDG will accumulate in a variety of benign bone tumors as well as inflammatory and traumatic pathology (Table 1). FDG has remained the primary radiotracer applied to musculoskeletal disease. Dynamic FDG PET with kinetic analysis (1) has helped to differentiate benign from malignant bone tumors as have measures of heterogeneity, which increase in osseous malignancy (2). Standardized uptake value (SUV) criteria alone lack specificity, although in one series using a cutoff of SUV 3, the sensitivity achieved was 97%, while the specificity was 67% (1). While ^{18}F sodium fluoride (NaF) has been long approved in the United States for human use, it has received less attention. Some work in metastatic disease has shown its exquisite sensitivity. Radiolabeled

amino acids may have utility in separating malignant from benign disease (3), but to date have not seen wide clinical use.

BENIGN BONE TUMORS

While many benign bone lesions show a relatively lower SUV than malignant bone tumors (4), chondroblastoma, giant cell tumors, fibrous dysplasias, eosinophilic granuloma, and aneurysmal bone cysts (4,5) show significant overlap with malignant lesions, likely because they contain giant cells and histiocytes (4,5).

Benign cartilaginous bone lesions tend to demonstrate low SUVs on FDG PET (6), although there have been some exceptions (5). Some studies suggest that an SUV of 2 can separate benign from malignant lesions. It is likely that a low SUV has a high positive predictive value for benignity. Only low-grade chondrosarcoma has been reported to overlap with benign cartilaginous lesions of bone.

Fibrous dysplasia, which may be mono-ostotic or polyostotic, has been reported to demonstrate variable uptake on FDG PET (7,8) (Fig. 1). The variable uptake in fibrous dysplasia has been postulated to reflect the various stages of fibroblast activity (8). Radiolabeled

Table 1 Benign Bone Tumors Positive on FDG PET

Tumor	CT characteristics	Clinical characteristics
Enchondroma (10)	Long, oval, well defined, expansile; diaphyseal, cortex thinned; chondroid calcification/matrix	3rd decade; tubular bones of hands and feet; diaphyseal; solitary; when multiple (Ollier's disease) or multiple with hemangiomas (Maffucci's syndrome)
Aneurysmal bone cysts (4)	Eccentric; "soap bubble," lytic; thin, eroded cortex; expansile, periosteal elevation; fluid/fluid levels in cystic spaces	More common in 2nd decade and females; common at metaphyses of lower extremity long bones
Fibrous dysplasia (variable uptake on FDG) (4, 8)	Expansile, endosteal scalloping, ground glass matrix	Polyostotic or mono ostotic; mostly occurs in ribs, femur, tibia, craniofacial bones; plain films highly specific
Nonossifying fibroma (3, 21)	Eccentric, intramedullary, abut the cortex, scalloped, >3 cm, sclerotic margin, central soft tissue density	3–42 yr; 70% in teenagers; risk of fracture if >50% of long bone diameter or >33 mm; also called fibroxanthoma
Eosinophilic granuloma (24)	Lytic, expansile lesion; sclerotic or ill-defined margin. May be multiple; homogeneously enhance	more common in 5–15-yr-olds; part of spectrum of langerhans cell histiocytosis; long or flat bones; usually asymptomatic but can present with pain or swelling; usually resolve in 3–24 mo
Avulsive cortical irregularity (77)	Medial distal femoral diaphysis, cortical roughening, lucent	Most often older children and adolescents; most common about the knee
Chondroblastoma (5, 78)	Lytic, cortical erosion, matrix mineralization, soft tissue extension, usually lower extremity; usually epiphyseal or apophyseal	Predominant males; 2nd decade of life; 1% of primary benign tumors; Ddx; differential diagnosis: giant cell tumors, aneurysmal bone cyst; clear cell chondrosarcoma; hemangioma; eosinophilic granuloma
Giant cell tumors (4)	Occur at articular ends of long bones and less frequently spine; lucent, expansile, marginal sclerosis; cortical destruction; extraosseous soft tissue	18–20% of benign tumors; peak age 20–40 yr; Ddx: brown tumors; chondroblastoma; malignant fibrous histiocytoma; aneurysmal bone cyst; variants of osteosarcoma
Sarcoidosis (24)	In small bones: lacy appearance, punched out cortical erosions; in large bones: lytic, lytic and sclerotic, or sclerotic (79, 80)	Peak 20–40 yr of age; associated with generalized involvement by sarcoidosis; tends to be a later manifestation
Exostosis (3)	Cortical or medullary bone protruding from metaphysis; continuity with metaphysis; cartilaginous cap may or may not mineralize (81)	2nd most common benign bone tumor; common at knee or proximal humerus; multiple or single; single with 1% incidence of malignancy; multiple has 3–5% incidence of malignancy

methionine has also shown accumulation in fibrous dysplasia (9).

Enchondromas are characterized on plain film by chondroid calcification (Fig. 1). They may either show low to moderate FDG uptake or no FDG uptake (3,10). They may be difficult to differentiate from low-grade chondrosarcomas. Osteochondromas will show mild uptake with FDG but may also be positive with radio-labeled amino acids (3,10). Nonossifying fibromas may show mild uptake (3,10) (Fig. 1).

Vertebral hemangiomas will show decreased uptake on FDG PET similar to what may be seen on bone scintigraphy (11). However, the typical "corduroy" appearance of the trabeculae on computed tomography (CT) (Fig. 2) will confirm the presence of a hemangioma.

Other benign entities such as fractures (12) and healing bone grafts (13, 14) will show increased uptake on either FDG or NaF PET. Insufficiency fractures occurring in a previous radiation port may be particularly problematic (Fig. 3) (12). Pathologic fractures may be difficult to differentiate from traumatic or insufficiency fractures, although dedicated CT or magnetic resonance imaging (MRI) may be useful.

MALIGNANT PRIMARY BONE TUMORS

Ewing's Sarcoma

Ewing's tumors encompass a spectrum of diseases including Ewing's sarcoma, primitive neuroectodermal tumors

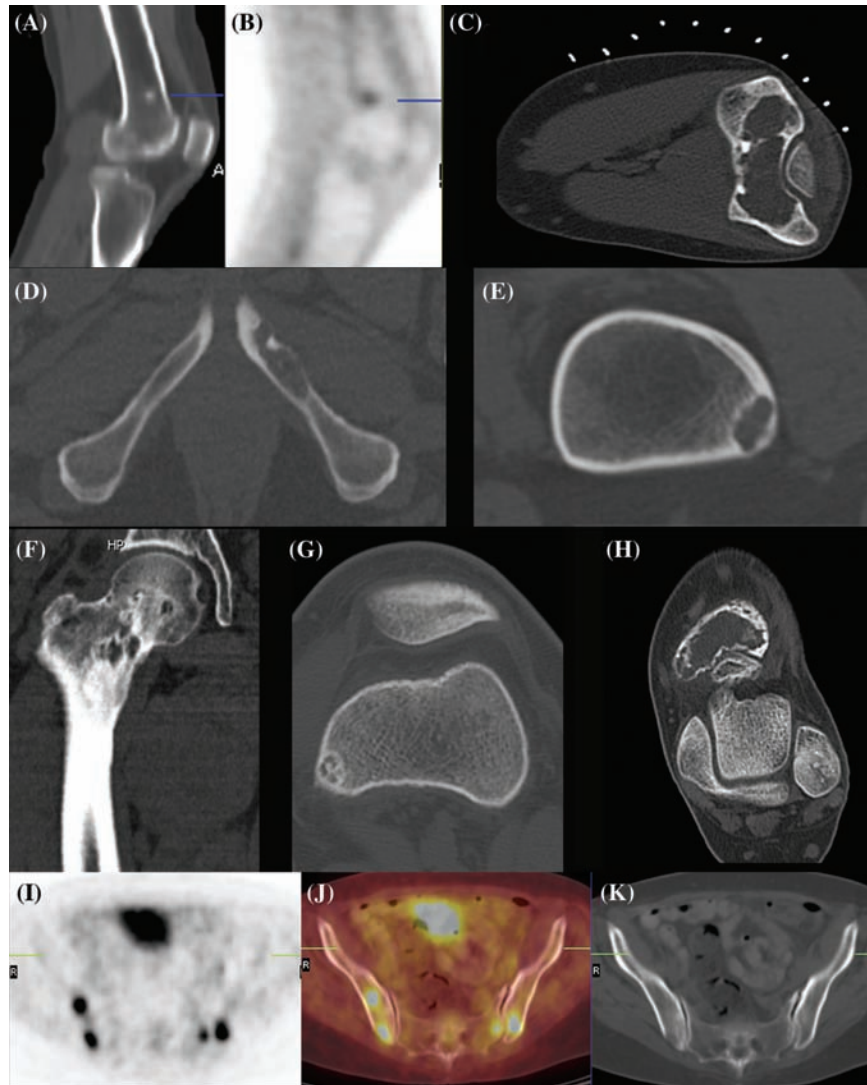


Figure 1 (A) Enchondroma of the distal femur, sagittal reconstruction of CT acquired during a PET/CT. (B) Enchondroma, corresponding FDG PET image. (C) Aneurysmal bone cyst, transaxial CT bone windows. (D) Fibrous dysplasia of the left pubic ramus, CT bone windows. (E) Nonossifying fibroma on CT. (F) Eosinophilic granuloma. (G) Fibrous cortical defect. (H) Chondroblastoma. Osseous sarcoid. (I) FDG PET, (J) fused PET and CT, (K) CT scan showing active, punched out lesions of sarcoidosis.

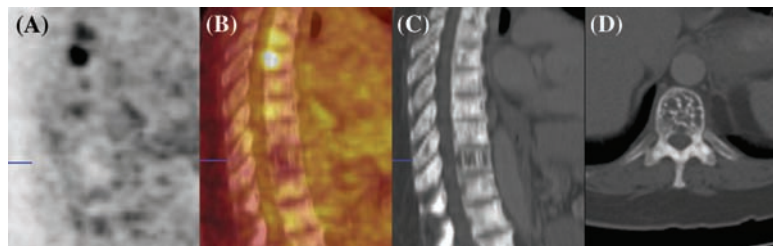


Figure 2 A 65-year-old man with lung carcinoma and mixed osteoblastic and lytic metastases. A hemangioma of the vertebral body has no uptake on (A) FDG PET as confirmed on the (B) fusion image. (C) The sagittal CT slice shows the appearance of “corduroy” trabeculae and fat density within. (D) The transaxial CT image shows the typical trabecular pattern associated with this entity.

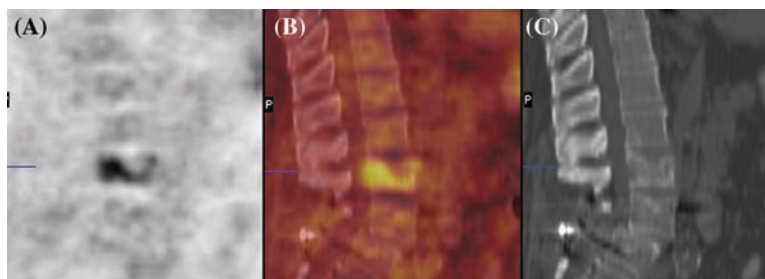


Figure 3 An 80-year-old man with a history of prostate cancer treated with radiation and a laminectomy of the lumbosacral spine, new back pain, and partial vertebral body collapse at L3, (A) FDG PET shows increased uptake at the fracture site superimposed in (B) the fusion image on the L3 vertebral body that shows collapse of the superior endplate on (C) CT.

(PNET), and atypical Ewing's sarcoma. PNET and atypical Ewing's sarcoma are characterized by neuronal markers which are not seen on Ewing's sarcoma. Tumors usually occur in the first or second decade and most commonly affect the bones of the pelvis or the metadiaphysis or diaphysis of long bones of the lower extremity (15). Identification of the extent of the primary tumor is critical to guide surgical management. Although skip lesions are rare, they augur a significantly worse prognosis (16). Metastases most frequently occur in the lungs and bones. The most significant predictors of outcome are tumor size and histologic response to preoperative chemotherapy (17).

The accepted treatment for Ewing's sarcoma currently is neoadjuvant chemotherapy followed by surgery, radiotherapy, and surgery where resection is incomplete, or radiation where resection is not possible, followed by additional chemotherapy (17). Presurgical radiation is sometimes employed instead of chemotherapy. The surgical approach to Ewing's involves an en bloc resection, which should include any skip lesions. Overall, 10-year survival with this approach is roughly 57%. Relapse generally occurs with metastatic disease rather than local recurrence (17).

Standard staging of primary Ewing's sarcoma and PNET include plain film, MRI, spiral CT of the chest, and bone scintigraphy. Bone marrow with or without reverse transcription polymerase chain reaction (RT-PCR) to detect occult marrow involvement is also used (17). CT of the primary may be employed but is not preferred to MRI.

A typical appearance of Ewing's sarcoma is a poorly margined, intramedullary process with aggressive periosteal reaction and associated soft tissue mass in a metadiaphyseal location (15). The periosteal reaction is most often laminated, but may be spiculated. Soft tissue calcification, cortical destruction, pathologic fractures, honeycombing, sclerosis, or cortical thickening are all more variable aspects. CT tends to show the size of the

soft tissue mass more accurately than plain film. On CT, Ewing's sarcoma usually appears as a large, ill defined, heterogeneous mass that displaces soft tissue (18). Densities will range from that of necrotic muscle to calcification. Both T1- and T2-weighted images will be heterogeneous owing to hemorrhage, necrosis, and calcification. The CT and radiographic differential for Ewing's sarcoma primarily includes osteomyelitis and osteogenic sarcoma. On occasion, bone scan may be more sensitive than plain film for the primary tumor. Three-phase scanning will show increase vascularity, hyperemia involving the bony and soft tissue component, as well as the delayed bone uptake.

FDG PET is a relatively new addition and its added value is uncertain at this juncture. Because Ewing's sarcoma is a high-grade malignancy, it is generally associated with increased FDG uptake (Fig. 4) (1,4,19), although SUVs may vary considerably and have been reported to range from 1 to 18 (20). As might be expected, smaller tumors tend to have lower measured SUVs, possibly because of partial volume effects. Sensitivity on a per-lesion basis for staging of primary Ewing's sarcoma has been found to be only 58% but on a per-patient/examination basis, 100% (20). Sensitivity of FDG PET for bone metastases from Ewing's sarcomas has been reported as 100% compared with 68% for bone scintigraphy (21). Sensitivity of PET alone for lung metastases smaller than 1 cm is poor (20). Nonetheless, as with other etiologies of lung metastases, PET/CT may improve detection. The change in FDG PET uptake in primary Ewing's sarcomas and PNET's after neoadjuvant chemotherapy has been shown to correlate with histologic response and to predict a better progression free survival with a cutoff of post treatment SUV of 2.5 for a mixed group of Ewing's sarcomas (22). Interestingly, progression-free survival (PFS) for all patients not stratified by post-chemotherapy SUV was similar to the cooperative study (17), but when stratified by SUV less than 2.5, PFS improved to 72% for patients regardless of metastatic status and 80% for those

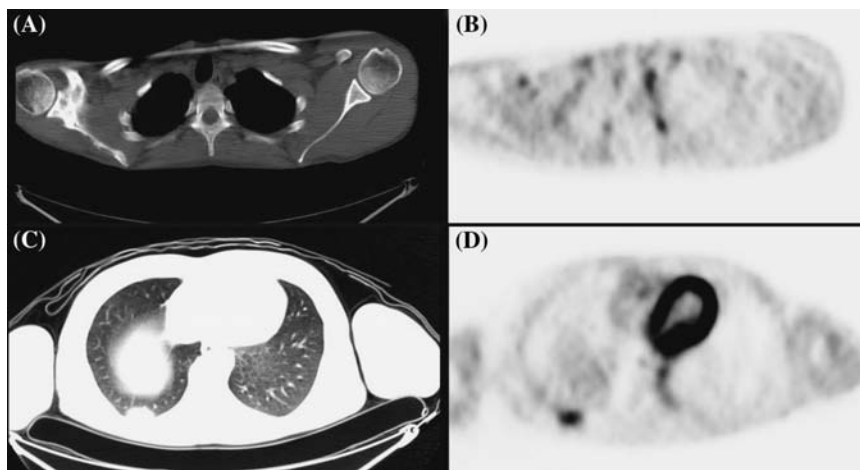


Figure 4 A 19-year-old male with a history of Ewing's sarcoma of the right glenoid, partially treated. (A) CT and corresponding slice from the simultaneously acquired (B) FDG PET shows minimal uptake in the right glenoid. However, a pleural based density (C) on CT scan showed intense focal uptake (D) on FDG PET consistent with metastasis.

with localized disease. As a practical matter, PET/CT has been useful in assessing the soft-tissue extent of tumor and in follow-up after neoadjuvant chemotherapy (23).

Osteogenic Sarcoma

Osteogenic sarcoma is primarily a disease afflicting young people, although there is a slightly lower incidence peak in people in their 40s and 50s. Osteosarcoma may arise in the metaphyses of long bones, but may also occur secondarily in Paget's disease, chondromas, and fibrous dysplasia. The vast majority of osteogenic sarcomas present with extension to the periosteum, but without metastases (24). Older age of the patient, histologic subtype, smaller tumor volume, and greater than 90% histologic response to neoadjuvant therapy signals a better prognosis (25,26). The presence of skip lesions also augur a poor prognosis although their incidence is low (27). The usual therapeutic approach consists of neoadjuvant chemotherapy, wide resection of the tumor, and adjuvant chemotherapy. This approach has resulted in a markedly increased survival for patients with osteogenic sarcoma (28).

Plain film remains a mainstay of assessment of primary osteogenic sarcomas, both for initial staging and assessment of response to therapy. On initial presentation, osteogenic sarcomas will be characterized by some periosteal reaction, cortical erosion, a lytic intramedullary component often with some amorphous calcification, soft tissue masses with variable calcification (29). With successful treatment, a reduction of volume in soft tissue and medullary cavity components, osteoid calcification of residual tumor, thickening of periosteal reaction, and increased sclerosis of bony tumor margins will be seen. Radiographically, decreases in soft tissue component and

a decrease in size carry only a 60% positive predictive value, while an increase in size has a very good correlation with poor histologic response (30). Occasionally, necrosis with fluid levels and debris may be seen on plain film (29).

Assessment by CT, noncontrast and intravenous contrast-enhanced, will focus on intramedullary tumor size measured in three orthogonal dimensions, extraosseous extension, and involvement of muscles, joints, blood vessels, and nerves (31). Spiral CT and 3D rendering may augment the measurement and depiction of the extent of tumor. Contrast enhancement is particularly important for the depiction of the soft tissue component (32). The appearance of osteosarcoma on CT is characterized by new bone formation and matrix calcification that tends to be denser centrally and decrease toward the periphery (Fig. 5) (18). On T1-weighted MRI, the signal intensity will exceed that of muscle, but is more variable in relation to muscle on T2. Both CT and MRI more often overestimate the size of the intramedullary component compared with pathologic examination. The sensitivity of CT, and even MRI, for skip lesions is low to moderate (27,31), but the sensitivity for intramedullary, cortical, and periosteal involvement is high. Sensitivity for articular involvement is about 70%, and for blood vessel and neural involvement only about 33%, although specificity is high (31). The clinical strength of CT lies in the detection of lung metastases (Fig. 5C) (28).

Although a multicenter cooperative group trial has shown little advantage of MRI over CT in evaluating the primary lesion, conventional dogma insists that MRI may give a better assessment of local extent and eventually response to therapy (33). T2-weighted MRI will demonstrate the necrotic cystic appearance associated

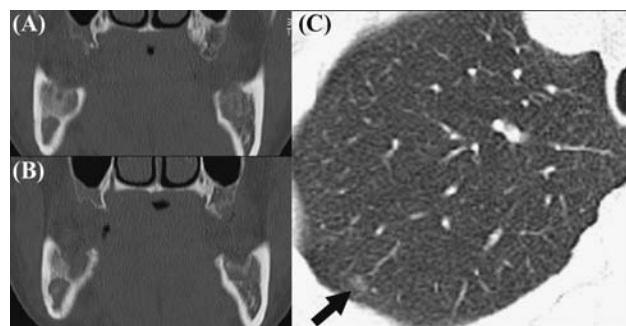


Figure 5 A 15-year-old girl with osteogenic sarcoma of the right mandible. (A) Coronal CT slices shows calcific matrix denser in the center and decreasing more peripherally with (B) periosteal reaction medially. (C) CT of the chest shows a small metastasis (arrow) in the posterior segment of the right upper lobe. This is far too small to be resolved on current FDG PET.

with residual tumor in the walls of the cysts and peritumoral edema (34,35). Changes in this edema on T2-weighted MRI provides a good assessment of tumor response (34). Dynamic imaging with gadolinium will reflect microvasculature and, at the end of chemotherapy, has been shown to be highly predictive of necrosis and response (36). However, false-positives do occur with fresh scar tissue (24). Diffusion-weighted MRI may have potential for assessing cellularity (37).

Static Tc-99m diphosphonate bone scans show a lower sensitivity for skip lesions than MRI but are useful for detecting distant osseous metastases (33). Bone scintigraphy is not sufficient for assessing tumor response although three-phase bone scans provide a slightly better assessment on the basis of changes in vascularity (38). In one comparison to dynamic gadolinium-enhanced MRI, three-phase scanning was of comparable value in assessing tumor response (39). In general, however, bone scintigraphy overestimates the extent of tumor and may show increased uptake with healing (40). Tc-99m sestamibi (41) and ²⁰¹Thallium scanning have both been used for detecting recurrence and assessing response to therapy, respectively. Although sestamibi may be slightly less sensitive than FDG PET, it may offer advantages in predicting response to chemotherapy in the metastatic/recurrence setting (41).

¹⁸F NaF accumulates in mineralizing bone by ionic exchanges with hydroxyl groups of hydroxyl apatite, offering a reflection of a process similar to conventional bone scintigraphy (42). Uptake in primary osteogenic sarcomas as well as metastases with a response in uptake to therapy has been reported, but the literature is extremely limited (24).

FDG PET offers a more specific indicator of tumor activity (33). SUV, specifically maximum SUV, because of the heterogeneity of osteogenic sarcomas (24), offers an

indication of the tumor grade (43,44). The heterogeneity seen on PET also underscores the value of this modality for directing biopsy (24,43). In terms of metabolic behavior there, nonetheless, remains a great deal of overlap between FDG PET SUVs and metabolic rates for osteogenic sarcomas and benign bone tumors. As an alternative to kinetic modeling, very delayed uptakes have also been used to assess the metabolism of osteosarcomas with a specificity of 76% and a sensitivity of 100% (45). On the other hand, there has been conjecture that metabolic rate derived from FDG PET may predict biologic behavior of these tumors better even than histologic grading (24,46). The degree of FDG uptake in an untreated primary has been shown to correlate with overall and disease-free survival in a small series of patients (47).

For staging of osteogenic sarcomas, CT remains the modality of choice for detecting lung metastases since FDG PET has only a 50% sensitivity in comparison with CT, the sensitivity of which was 75% in the same series (48). PET's only use in that the setting might be to confirm the malignant nature of a CT-detected nodule. Potentially, FDG PET might be useful in detecting skip lesions, which has been suggested by only one series (24,49). The literature is too limited on the detection of bone metastases to be conclusive, but reports of negative FDG PET results exist (21,50) and MRI or bone scintigraphy appears to be a more sensitive method.

FDG PET may play a more effective and important role in assessing outcome of neoadjuvant chemotherapy. Histologically, a good response, constituted by greater than 90% necrosis or less than 10% viable cells predicts an improved disease-free survival. A number of studies have shown that, in general, changes in FDG PET correlate with histologic tumor responses in the neoadjuvant setting (51,52). Simply using changes in visual analysis or tumor to background ratios, PET performed at the end of chemotherapy and prior to surgery had an excellent negative predictive value for response and 87% positive predictive value for response. Calculation of percent changes was less helpful in predicting a good response. Franzius et al. showed a greater than 30% decrease in tumor to nontumor ratios at the completion of chemotherapy in good responders and increasing ratios in the two nonresponders in their series (40). Using the ratio of pretreatment SUV to post neoadjuvant chemotherapy SUV, Hawkins et al. showed a positive correlation with a good tumor response but found no threshold for either posttreatment SUV or ratio that could be used with reliability (53). Schulte et al. also showed a high positive predictive value for good tumor response using this ratio with a cutoff of 0.6 and moderately high negative predictive value (8/10 patients) (52). FDG PET after only one cycle of chemotherapy may potentially predict response

but has not yet been studied extensively (54). False positive uptake during or after neoadjuvant chemotherapy has been described in biopsy scars and in the newly formed fibrous capsules that are part of the healing process (54). Residual uptake in treated osteosarcomas is common even with good response (43,54).

For monitoring recurrence, a combination of FDG PET, CT of the chest and MRI may be needed (24). While MRI has a reported sensitivity of 80% to 85% for local recurrence (55), FDG PET has been used to detect local recurrence (41,56) with a 98% sensitivity and 90% specificity in one series (41). In a comparison of FDG PET with a combination of MRI, chest CT, and bone scintigraphy, PET showed a sensitivity of 93% and specificity of 76% on a per-patient basis compared with 100% sensitivity for conventional imaging and specificity of 36% (57). The sensitivity of PET for local recurrence and osseous involvement was comparable to the other modalities, but specificity was higher. For pulmonary metastases in this setting, FDG PET was less sensitive than chest CT but also less specific, presumably, PET/CT might help avoid the latter. It remains to be seen whether the CT obtained with PET/CT will provide adequate sensitivity for pulmonary metastases compared with a dedicated diagnostic chest CT scan.

Chondrosarcoma

Chondrosarcomas more often occur in men and in patients over 50 years old. They arise in bone or may be associated with exostoses. They are common tumors in the chest walls and in paravertebral locations (18).

The typical appearance of chondrosarcoma on CT is a lobulated, soft tissue density mass with chondroid calcification within it (Fig. 6). Variably, bone destruction and soft tissue masses are seen (18). On MRI, T2-weighted imaging will show signal intensity somewhat higher than fat. On T1, density is similar to that of muscle. The chondroid matrix within the tumor is likely to cause signal void on MRI. Gadolinium enhancement is often heterogeneous or peripheral.

Chondrosarcomas are in general, but not uniformly, FDG avid (Fig. 6) (10,58). With the exception of low-grade chondrosarcomas, they have been reported to have high SUVs making FDG PET a potentially important adjunct to the evaluation of cartilaginous bone tumors both because chondrosarcomas may be clinically asymptomatic and histopathology of tumors may be inconclusive (6). Low-grade chondrosarcomas have been found to be indistinguishable from benign cartilaginous tumors based on SUV (10). SUV has been reported to correlate with grade (4,6,10). In one study using an SUV cutoff of 2.3, FDG PET had a positive predictive value of 82% for high grade and a negative predictive value of 96% (10). The combination of SUV and histopathologic grading has been reported to have prognostic significance (58). In fact, a higher pretreatment SUV (>4.0) predicts recurrence or metastasis with a 90% sensitivity, 64% positive predictive value, and 94% negative predictive value (58). Conversely, the lower the SUV, the longer the disease-free survival. However, in the study by Lee et al. (10), an elevated SUV predicted metastasis but not recurrence. When these tumors recur or metastasize, their metabolic characteristics may differ from the original primary tumor (6).

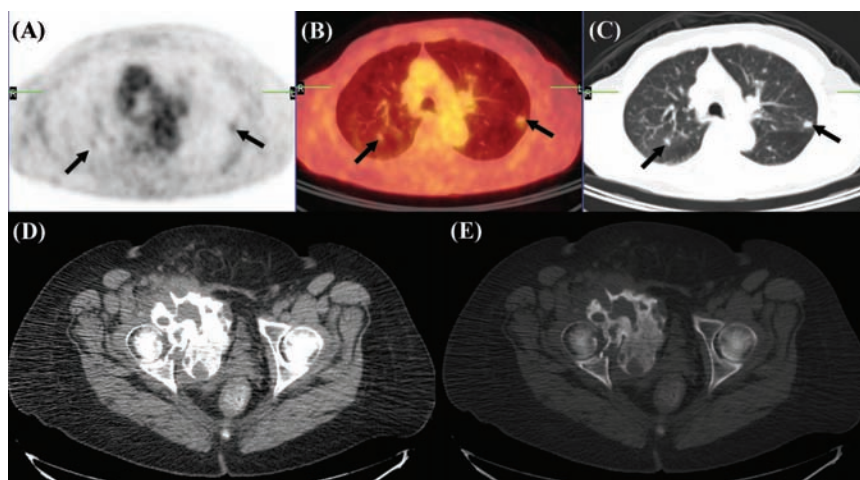


Figure 6 A 78-year-old man with a chondrosarcoma of the pelvis and pulmonary metastases (arrows). (A) Transaxial FDG PET, (B) Fused PET and CT, and (C) lung windows demonstrate increased FDG uptake fusing to a left upper lobe pulmonary metastasis. CT, soft tissue window (D), and bone window (E) show a pelvic mass with chondroid matrix arising from the right acetabulum.

Multiple Myeloma

Multiple myeloma is characterized clinically by the proliferation of plasma cells with the over-production of immunoglobulins. Clinical manifestations may include the complications of the paraproteinemia and/or bone marrow or bone lesions with impaired renal function, hypercalcemia, recurrent infections, anemia, sequelae of hyperviscosity, bone pain, fractures, and neurologic syndromes secondary to spinal involvement (59). The diagnosis of multiple myeloma requires the documentation of a monoclonal protein in serum and/or urine, the presence of bone lesions, and an increased number of plasma cells in the marrow. Nonetheless, about 3% of patients will not demonstrate the paraprotein in urine or serum, the so-called nonsecretory myeloma. On the other hand, the presence of a paraprotein is not sufficient to establish the diagnosis of multiple myeloma and can be seen in monoclonal gammopathy of undetermined significance (MGUS), amyloidosis, solitary plasmacytoma, chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma (59). MGUS, in particular, has only a 1% incidence of progression to myeloma and usually does not require treatment. Solitary plasmacytoma is often treated with external beam radiotherapy alone while symptomatic multiple myeloma requires chemotherapy.

Staging of myeloma depends on the presence of symptoms and the number of bone lesions detected according to the recently adopted Durie/Salmon PLUS system (Table 2) (60). Seventy percent of patients with multiple myeloma will be symptomatic. While radiographic skeletal survey was, for many years, the mainstay of skeletal evaluation, CT is recognized as being more sensitive for bone lesions than plain film (60,61). The hallmark of lesions on CT are lytic, "punched out" lesions in the flat bones or long bones (60). In the spine, CT is useful for assessing fracture risk. Careful attention to CT technique is important to optimize the sensitivity of CT (62). CT, as well as MRI and PET/CT, all have the added advantage of demonstrating extramedullary disease, which carries a worse prognosis (63). MRI performed using T1-weighted and inversion recovery sequences is useful for identifying

focal marrow lesions as well as diffuse marrow disease (60). Also, in the presence of neurologic symptoms, MRI is the preferred method to evaluate the spinal canal and cord. Gadolinium is usually reserved for assessment of treated disease to differentiate active disease from effectively treated tumor (64). Conventional bone scintigraphy is notoriously insensitive for myeloma, but more recent exploration of Tc-99m sestamibi has shown higher sensitivity than skeletal surveys and even slightly higher than PET (65). In fact, sestamibi uptake in that series of patients showed a better correlation with the degree of marrow plasma cell infiltrate.

While PET using ^{11}C -Choline in myeloma has been reported to be positive, FDG remains the clinical mainstay of PET imaging in myeloma (Fig. 7) (66). FDG PET, and now PET/CT, has been incorporated into the Durie/Salmon PLUS system of staging. While MRI may sometimes detect lesions not seen on PET/CT, PET/CT will detect lesions beyond the anatomic scope of an MRI (67) and is more sensitive than skeletal surveys (63,67).

Table 2 Staging of Multiple Myeloma

Stage	Criteria
Stage IA	Asymptomatic with one bone lesion
Stage IB	Symptomatic with no more than 4 bony lesions or mild diffuse marrow disease by MRI
Stage II	Symptomatic with 5–20 bone lesions or moderate diffuse spinal marrow signal on T1 MRI
Stage III	Symptomatic with >20 bone lesions and/or diffusely marrow signal on T1 MRI

Source: From Ref. 60.

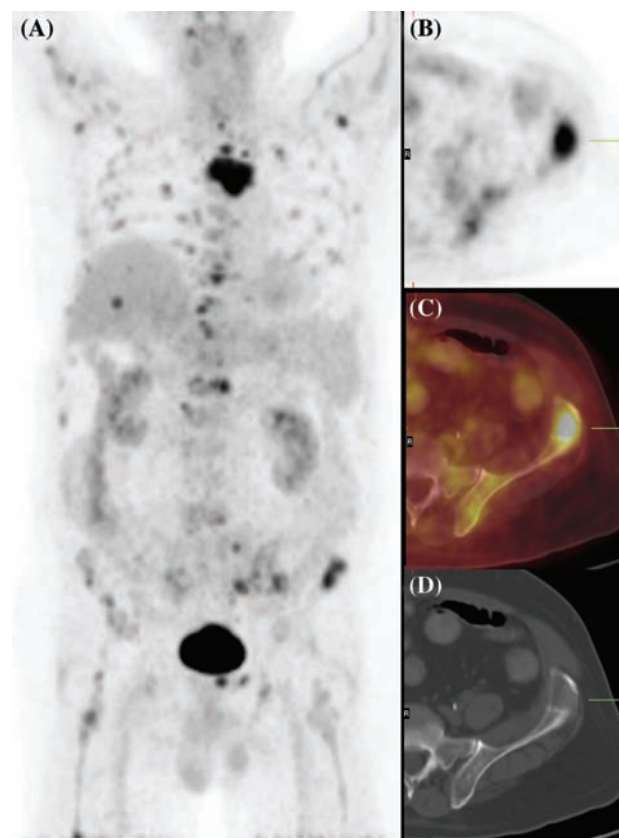


Figure 7 A 73-year-old man with multiple myeloma. (A) The anterior view from the MIP shows multiple foci of increased uptake. The lytic lesion in the left iliac bone on (B) PET and the corresponding (C) fusion image shows intense FDG accumulation. (D) The corresponding CT slice image shows the typical lytic lesion of myeloma.

Bredella et al. has reported an 85% sensitivity and a 92% specificity for FDG PET alone (68). Although Breyer et al. first suggested using an SUV cut-off of 2.5, in their patients lesions with lower SUVs were present on re-review of images (62). Clearly, a high index of suspicion for any uptake is helpful. In one series of patients, PET/CT detected new or previously unrecognized soft tissue or bone lesions in over half the patients and management was changed in a similar percentage when PET/CT was added to the evaluation of multiple myeloma patients (62). Upstaging of patients by PET/CT has been reported in 27% to 37% of patients studied (62,68,69). PET/CT may also show diffuse marrow uptake consistent with diffuse bone marrow involvement, although MRI appears to be more sensitive for this (62,63,67). On the other hand, a negative PET/CT suggesting stable MGUS reliably supports the use of continued surveillance rather than treatment (63). The identification of a single plasmacytoma as opposed to frank multiple myeloma on PET/CT predicts a longer survival (62). PET/CT plays a particularly useful role in patients with nonsecretory disease, in whom the usual laboratory tests are unhelpful (62,63).

Finally, PET/CT to monitor the occurrence of relapse and response to treatment appears to provide reliable prognostic information (63,68,70) although immunosuppressive therapy may decrease uptake (68) and can direct

continued treatment. For instance, a focal relapse may be handled with local external beam radiation.

FDG PET has also found incidental utility in the diagnosis of infections in these chronically immunosuppressed patients. While myeloma may occur in extramedullary sites, a nonmedullary uptake also raises the possibility of infection (71). Similarly, bone uptake that crosses a joint or involves a joint primarily is less likely to represent a myelomatous process per se. In a series of 248 patients with potentially nonmyelomatous uptake on FDG PET, 165 sites of infection were identified and 18% were clinically silent. FDG PET also accurately showed resolution of these infections.

Primary Lymphoma of Bone

Although primary lymphoma of bone is a relatively rare tumor (72) and a relatively rare form of non-Hodgkin's lymphoma (73), FDG PET may be used more frequently than in other primary bone tumors simply because of third party reimbursement patterns in the United States. Primary lymphoma of bone occurs in children and adults and in relatively large series, median age of presentation has been reported to be 48 to 55 (73,74). In those series, the most common histology was diffuse large cell lymphoma. Only a relatively small percentage, 13% in one series (73),

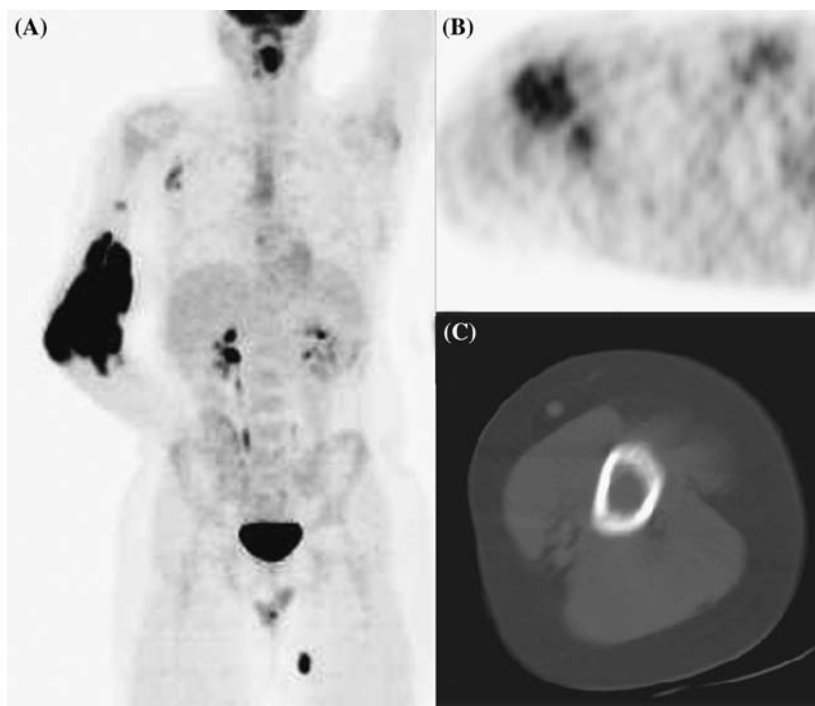


Figure 8 A 14-year-old boy who presented with right arm pain. Anterior view of a maximum intensity projection from (A) the FDG PET shows intense uptake in the bone and adjacent soft tissue. Other sites of lymphoma were present. (B) Transaxial PET and (C) CT through the distal diaphysis of the right humerus shows increased uptake and a permeative pattern in the anteromedial cortex of the humerus.

was polyostotic. The most common presenting symptom was pain with a frequent incidence of fracture. Most patients presented with early stages and five-year overall survival was 88% with a significant survival advantage for patients treated with combined chemotherapy and radiation therapy over a single modality. Secondary bone lymphoma may occur in the presence of a systemic disease or may present first with bone involvement and then relatively early extraosseous involvement (75). While this occurs more commonly than primary lymphoma of bone, the incidence of bone involvement (rather than bone marrow involvement) is still relatively rare (75).

Primary lymphoma of bone more often occurs in the metadiaphysis of long bones (Fig. 8). Although MRI is currently the morphologic imaging modality of choice, CT will show an aggressive, permeative lytic destructive lesion, although about one-third of these present with mixed lytic and blastic patterns; and a very small percentage will show primarily a blastic lesion (76). In Hodgkin's disease, which is rarer than non-Hodgkin's bone lymphoma, lytic patterns occur more often than blastic. Periosteal reaction, soft-tissue masses and cortical destruction are common. Sequestra may be seen on CT. Regional lymph node involvement is not a frequent occurrence. FDG PET has been useful in demonstrating other sites of disease, following response to therapy and identifying early relapse (72).

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PET/CT Evaluation of Soft Tissue Sarcoma

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INTRODUCTION

Soft tissue sarcomas are relatively uncommon, accounting for 1% to 1.5% of cancers in the adult population of the developed world (1,2). In the pediatric population, they represent a slightly higher percentage of malignancies. They vary widely in their clinical behavior and their histology (Table 1). One of the challenges is to distinguish benign soft tissue tumors from malignant sarcomas.

In general, prognosis at the initial staging is determined by histologic grade, tumor size, surgical resectability, and nodal or distant metastases (Tables 2 and 3), although nodal metastases are uncommon (3, 4). Clinical evaluation of patients should include a thorough medical history and physical examination and imaging. Biopsy to obtain histology needs to be planned carefully to avoid seeding of tumor along the biopsy tract and to obtain the highest-grade portion of the tumor (5). Imaging, both structural and metabolic, plays important roles in assessing the initial approach to therapy, initial staging, and in the follow-up for recurrence and/or development of metastases. Plain film can assess deformity or involvement of the bone. Although there is no statistical difference in the evaluation of the primary provided by computed tomography (CT) versus magnetic resonance imaging (MRI), MRI appears to be preferred (Fig. 1) (6). Either CT or MRI of the tumor or mass helps determine the extent of

the lesion, its relation to the neurovascular structures, and to bone. Chest CT should be performed to identify lung metastases especially in patients with large tumors or with high-grade malignancy (Fig. 2) (7). PET/CT is increasingly a part of this evaluation for staging, identifying biopsy sites, prognosis, response to therapy, and identifying local or distant recurrence. A number of PET radiotracers have been used to assess soft tissue sarcomas. Although FDG remains the mainstay because of its clinical availability, fluorothymidine has been used successfully to identify primary and metastatic lesions with a correlation between tumor grade and uptake (8). ^{18}F fluoromisonidazole has been used in a very limited fashion to assess hypoxia in tumors. In soft tissue sarcomas, heterogeneous uptake suggests differences in oxygenation within the tumors (9). ^{11}C tyrosine has been used to assess tumor response to interferon therapy with better accuracy than FDG (10). ^{11}C choline has been reported to be useful in staging of soft tissue sarcomas with more accurate TNM staging, 94% compared with 60% for conventional imaging (11).

The treatment of sarcoma involves as near complete as possible surgical resection supplemented by chemotherapy and radiation therapy. Chemotherapy may be used in the neoadjuvant setting to attempt to reduce the tumor to a surgically manageable one or may be used with or without radiation in the adjuvant setting when macroscopic or microscopic disease may be left behind.

Table 1 Classification of Soft Tissue Sarcoma

Type	Subclasses	Gender prevalence	Peakage incidence	Overall survival
Malignant fibrous histiocytoma (fibrosarcoma)	Storiform Myxoid Giant cell Inflammatory	Male	Late adult	53% (22) to 64% (4)
Liposarcoma	Well differentiated Myxoid Round cell Dedifferentiated Pleomorphic	Equal Equal Equal Equal Equal	Mid-late adult Mid-late adult Mid-late adult Mid-late adult Sixth decade >50 yr	90% (12) 70% (38) 40% (38) 70% ^a (12,31) 40% (32) to 59% (40)
Synovial sarcoma	Biphasic Monophasic epithelial Monophasic fibrous	Female	Adolescent to young adult (4,44)	55% (155)
Neurofibrosarcoma	Malignant schwannoma Glandular malignant schwannoma Malignant epithelioid schwannoma Malignant Triton schwannoma (53)	Female	Young adult	41% (51) to 83% (4) 10% with metastases (51) 80% with complete resection (51) 14% with incomplete resection (51)
Leiomyosarcoma		Male	5th–6th decade	51% (4) 46–64% (56)
Clear cell sarcoma		Equal	Young adults	48–59% (4,60)
Fibrosarcoma	Infantile (65) Adult type (156): Low-grade myxofibrosarcoma Low-grade fibromyxoid sarcoma Hyalinizing spindle cell tumour with giant collagen rosettes Sclerosing epithelioid fibrosarcoma	Male Equal Equal Equal Equal	Children 5th decade 5th decade (156) 4th decade (156)	80–85% (4,65)
Rhabdomyosarcoma	Alveolar Embryonal Pleomorphic	Female Female Female	>6 yr <6 yr Adults 10–35 yr (72)	84% (4) 67% (69) 41% (69) 25% (78) to 89% (4)
Epithelioid sarcomas		Male (75)	Adults (3rd decade)	62% (4) 71% (81)
Alveolar soft part sarcomas		Female		91% (4), 59% (158)
Vascular sarcomas	Angiosarcoma, Cutaneous (157) Kaposi sarcoma Epithelioid hemangioendothelioma	Female Male Male	Elderly 5th–7th decade Variable	10–20% (157) 100% (117) ^b 15% (159) ^c 60% (lungs) (160) ~100% (115)

^aExtremity lesions.^bIndolent form.^cImmunocompromised.

Source: From Ref. 4.

DIFFERENTIATING BENIGN FROM MALIGNANT TUMORS

In general, benign soft tissue lesions far outnumber malignant ones (5). Conventional MRI may not always differen-

tiate between benign and malignant lesions (5). Certain features may sway the reader toward malignancy over benignity; for example, the presence of calcification, or soft tissue nodularity in a lipomatous tumor on CT (12). Dynamic contrast enhance MRI (DCE-MRI) has been

Table 2 Staging of Soft Tissue Sarcomas (Musculoskeletal Tumor Society)

Stage	TNM
Stage IA	G1, T1, M0
Stage IB	G1, T2, M0
Stage IIA	G2, T1, M0
Stage IIB	G2, T2, M0
Stage III	Any G, any T, M1

Abbreviations: G1, low histologic grade; G2, high histologic grade; T1, confined to a compartment; T2, extracompartamental; M0, absence of metastases; M1, presence of metastases.

Source: From Ref. 154.

Table 3 Staging of Soft Tissue Sarcomas (AJCC)

Stage	TNM
Stage I—low grade, superficial, and deep	G1, T1a, N0, M0 G1, T1b, N0, M0 G1, T2a, N0, M0 G1, T2b, N0, M0 G2, T1a, N0, M0 G2, T1b, N0, M0 G2, T2a, N0, M0 G2, T2b, N0, M0
Stage II—high grade, superficial, and deep	G3, T1a, N0, M0 G3, T1b, N0, M0 G3, T2a, N0, M0 G4, T1a, N0, M0 G4, T1b, N0, M0 G4, T2a, N0, M0
Stage III—high grade, large, and deep	G3, T2b, N0, M0 G4, T2b, N0, M0
Stage IV—metastases to lymph nodes or distant sites	Any G, any T, N1, M0 Any G, any T, N0, M1

For tumor grade, GX indicates grade cannot be assessed; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; and G4, poorly differentiated or undifferentiated. For primary tumor, TX indicates primary tumor cannot be assessed; T0, no evidence of primary tumor; T1, tumor ≤ 5 cm in greatest dimension; T1a, superficial tumor; T1b, deep tumor; T2, tumor > 5 cm in greatest dimension; T2a, superficial tumor; and T2b, deep tumor. For regional lymph nodes, NX indicates regional lymph nodes cannot be assessed; N0, no regional lymph node metastasis; and N1, regional lymph node metastasis. For distant metastases, MX indicates distant metastasis cannot be assessed; M0, no distant metastasis; M1, distant metastasis.

Abbreviation: AJCC, American Joint Committee on Cancer.

Source: From Ref. 7.

shown to be helpful in determining whether a lesion is benign or malignant. Early and rapid enhancement are indicators of malignancy (13). Using the ratio of enhancement at one minute to enhancement at two minutes after injection of contrast and the slope of the curve derived from DCE-MRI, accuracy of 95% has been achieved in differentiating benign from malignant soft tissue tumors (13).

FDG PET by visual analysis alone is inaccurate for differentiating between benign and malignant lesions with

false-positive uptake reported in a hibernoma (14), schwannoma (15), inflammatory lesions (16), scar tissue, and infection (17). False negatives have been seen in low-grade sarcomas (16). Standardized uptake value (SUV) thresholds have been identified that are helpful in differentiating benign from intermediate or high-grade sarcomas, but not low grade (16). Although, in the case of differentiating lipoma from well-differentiated liposarcoma, PET has shown only minimal value since the uptake will be low. In patients with neurofibromatosis, FDG PET has been useful in detecting malignant transformation in plexiform neurofibromas (18,19).

Delayed FDG PET at four hours after injection has shown improved discrimination with a 100% sensitivity and 76% specificity for malignancy using an SUV of 3 at four hours (20). Furthermore, uptake by benign lesions plateaus or even decreases after two hours (20). Kinetic modeling has also provided a means of distinguishing between benign and malignant soft tissue sarcomas (20).

CLINICAL AND CONVENTIONAL IMAGING CHARACTERISTICS OF SOFT TISSUE SARCOMAS

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFH) is one of the more common soft tissue sarcomas, presenting with a painless, enlarging mass centered on muscle or surrounding fascia (4,21). They occur more often in the proximal extremity, pelvis, or trunk, and may involve adjacent bone (4). Soft tissue or osseous MFH has been associated with previous radiation exposure (22), bone infarcts, Paget's disease, prolonged corticosteroid use, or even arthroplasty (23–26). While the soft tissue MFHs tend to arise from striated muscle, the cutaneous form called atypical xanthofibroma may not extend beyond the subcutaneous tissues (27). On CT scan, they will appear heterogeneous and will enhance with contrast (21). On MRI, T1-weighted images will show heterogeneous signal intensity lower than that of muscle and on T2-weighted imaging, intensity similar or greater than fatty tissue (21). MFH is characterized on MRI by poor margin definition and internal low signal septation (28).

As with most soft tissue sarcomas, treatment with wide excision and clean margins offers the best result. Adjuvant chemotherapy has given good clinical results (22). MFH appears to be relatively less responsive to radiation (22,29).

Liposarcoma

Liposarcoma shows the second highest prevalence among soft tissue sarcomas constituting 10% to 35% (12). While liposarcomas also tend to occur in the trunk and extremities, they have a slightly greater predilection for distal extremities compared with MFH (4). Liposarcoma

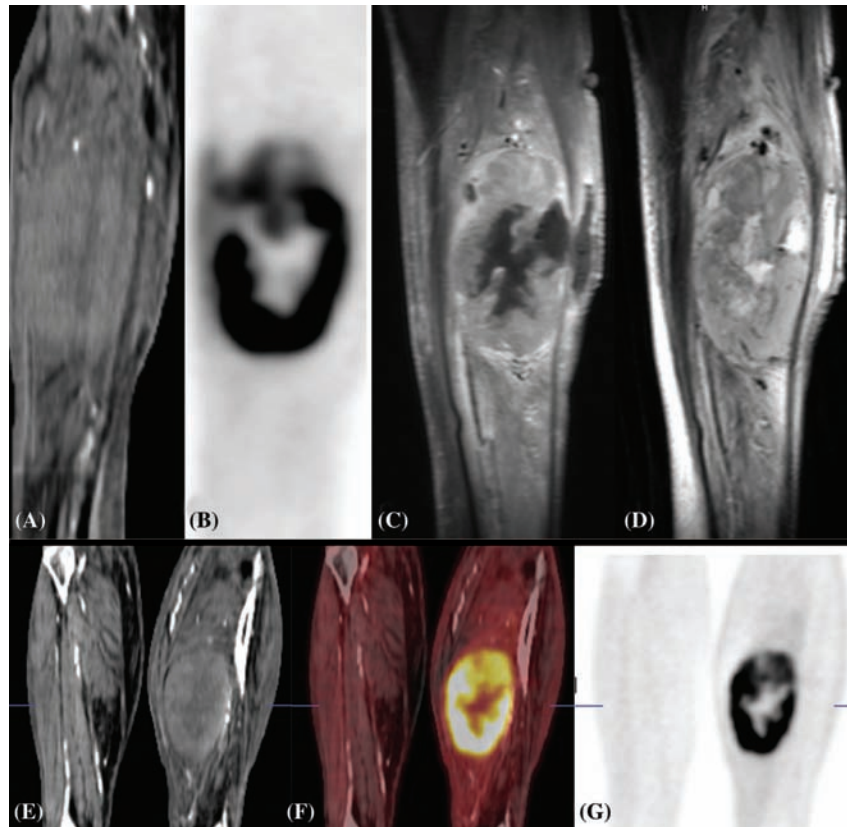


Figure 1 A 75-year-old man with recent development of a rapidly growing soft tissue mass of the calf. Biopsy revealed a high-grade sarcoma, not otherwise specified. (A) CT sagittal reformatted image, acquired as part of the PET/CT, shows a poorly defined soft tissue mass occupying and expanding the calf muscles. (B) Corresponding sagittal FDG PET shows the highly active tumor (SUVmax 12.3) with a relatively hypometabolic center. Also, PET shows extension of activity posteriorly along fascial planes that are ill-defined on CT. (C) On a contrast-enhanced T1 fat-suppressed sagittal MR image, the hypometabolic area is seen to correspond to the nonenhancing, irregular, central area consistent with necrosis surrounded by the moderately enhancing tumor which extends to the fascial plane into the subcutaneous tissue. (D) A sagittal STIR MR image shows high signal consistent with central pockets of necrosis as well as heterogeneously high signal throughout the viable tumor. The MR images provide a much clearer picture of the extent of the tumor than (A) the noncontrast CT. In this case, the PET suggests involvement extending into the adjacent subcutaneous fat posteriorly. (E) Coronal CT in this patient demonstrates a more clearly delineated, well-circumscribed soft tissue mass in the left calf with central low-density areas. (F) Corresponding fused and (G) FDG PET show the intense and heterogeneous uptake with a hypometabolic area in the center, generally corresponding to areas of necrosis on the CT.

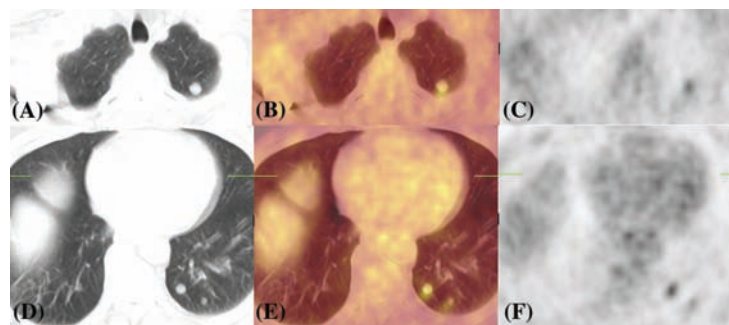


Figure 2 A 64-year-old man with a history of an unspecified soft tissue sarcoma previously treated with surgery and chemotherapy. FDG PET/CT was performed to monitor for recurrence. (Top row) (A) CT, (B) fused, and (C) PET images show the typical appearance of a well-defined, smooth-margined lesion consistent with a metastasis in the right apex that demonstrates FDG PET activity in spite of its relatively small size. (Bottom row) (D) CT, (E) fused, and (F) FDG PET show two lesions in the left lower lobe also typical of pulmonary metastases in this patient. These metastases also demonstrate FDG avidity in spite of their relatively small size.

includes a spectrum of pathology that extends from lipoma to atypical lipomatous tumors to well-differentiated liposarcoma to the other subgroups listed in the Table 1. Even the more benign end of the spectrum is subject to local recurrence and to degeneration into more malignant cell types (30). Well-differentiated liposarcomas are the most common of these tumors encountered. Clinically, these are likely to present as painless, enlarging masses that are intra-, intermuscular, or subcutaneous (12). Histologically, atypical lipomas and well-differentiated sarcomas are identical, but may be termed atypical lipomatous tumors when they occur in the subcutaneous tissues (12). Dedifferentiated liposarcomas demonstrate both a well-differentiated liposarcomatous component and a nonfat sarcomatous component. These are most often found either at sites of local recurrence of the well-differentiated liposarcomas or as a result of spontaneous malignant dedifferentiation in a well-differentiated liposarcoma often with a lag phase of seven to eight years (12). A rapid enlargement of a previously identified fat-containing mass may be the harbinger of dedifferentiation. They more often occur in the retroperitoneum than the extremities.

Myxoid liposarcomas appear to be part of a pathologic continuum with round cell liposarcomas and constitute 20% to 50% of liposarcomas (12,31). The myxoid component is considered intermediate grade, but the round cell component carries a more aggressive high-grade characterization (31). While they are rare in children, they are still the most common form of liposarcoma in the pediatric age group (12). They also present most commonly as a very large, but painless mass in the extremities.

Pleomorphic liposarcomas are high-grade tumors with that tend to affect the lower extremity, but are the least common of all the liposarcomas (12,31,32).

On CT and MRI, benign lipomas qualitatively show a high percentage of fat (>75%) in most cases (30). Atypical lipomas show a more mixed soft tissue/fat composition and liposarcomas tend to have no fat or less than 75% fat. In these tumors, soft tissue components tend to be nodular or confluent masses (30). While thickened septa have been described across the spectrum of disease, any soft tissue nodularity should raise the suspicion of liposarcoma (12). These soft tissue components should have a high signal intensity on T-2 weighted spin echo, STIR, or fat-suppressed T-2 weighted MR images and in one series showed a 77% specificity for liposarcoma (33,34). Most well-differentiated liposarcomas will show gadolinium enhancement (35). A low percentage, 10% to 32%, of well-differentiated liposarcomas/atypical lipomatous tumors will show calcification on CT (12). Dedifferentiated liposarcomas on CT will show calcification, water density, and fat. On MRI, they will be similar to well-differentiated liposarcoma except that the nodular components tend to be larger.

Myxoid/round cell liposarcomas typically present on CT as large masses with water density components that appear cyst-like, corresponding to the myxoid portion of the tumor, soft tissue components corresponding to the round cell histology, and fat density, although there is usually less fat in these tumors than other liposarcomas. They are generally intermuscular, multilobular, and well defined. They show low signal intensity on T1-weighted MRI and high signal intensity on T2-weighted MRI. The nonfatty portions of the tumor demonstrate contrast enhancement in the vast majority of cases (36) and these tumors tend to show greater degrees of heterogeneity (12,31).

On both CT and MRI, pleomorphic liposarcomas show marked heterogeneity with elements of hemorrhage, and necrosis is commonly seen (31,37). Fatty density or signal may not be prominent, but small foci of fat do occur in a considerable number of cases (12,34).

When well-differentiated liposarcomas and atypical lipomas are treated with wide surgical excision, local recurrence rates are low. For that reason these tumors have a better prognosis in the extremities. However, when complete excision is not possible, the risk of recurrence and de-differentiation increases (33). Unlike MFH, liposarcomas appear to be fairly responsive to radiation therapy, which will be used when complete excision is not possible (12,29).

Dedifferentiated liposarcomas have a high recurrence rate (41%) and significant incidence of distant metastases, up to 20% to liver, lung, or bone and a mortality of up to 30% (31). They are treated with surgical excision followed by radiation and then often by chemotherapy (12).

Myxoid liposarcomas have a greater tendency to metastasize outside the lungs to soft tissues and the mortality is determined by the degree of round cell tumor (38). Treatment of myxoid liposarcomas includes wide surgical excision followed by radiation. Adjuvant chemotherapy is a more variable component of the treatment regimen (39).

Pleomorphic liposarcomas have a high rate of metastasis (31). Treatment involves surgery, radiation, and chemotherapy with recent improvements in survival, as high as 59% at five years, with ifosfamide-containing regimens (40).

Synovial Sarcoma

Synovial sarcomas are the second most common sarcoma in children and adolescents after rhabdomyosarcoma (41) and account for about 8% of soft tissue sarcomas in adults (42). Synovial sarcomas occur in proximity to joints, ligaments, and tendons, but they do not appear to arise from synovium per se (4). Unlike other sarcomas, they tend to be painful and may not present with a mass (42). The most common location is the lower extremity, usually near the knee (42). They may start out slowly with a relatively indolent course over a number of years, but then

will become more aggressive. Metastases are present in up to one-fourth of patients at presentation (43). They may be associated with irregular soft tissue calcification (4,42). In addition to calcification, CT scans may show necrosis, hemorrhagic, or cystic components with nodularity of the walls, which enhance with contrast (42). The erosion of bone that may accompany these tumors does not usually appear aggressive with a small percentage of tumors showing medullary invasion (42,44). MR images of synovial sarcomas will show frequently well-circumscribed, multilobulated lesions that are hypointense relative to muscle on T1 imaging with areas of increased signal intensity on both T1- and T2-weighted imaging representing hemorrhage. When they are large, they are more frequently heterogeneous on T2-weighted MR images consistent with fluid, fat, and fibrous elements. The “triple sign” of low, high, and intermediate signal on T2-weighted images reflects this heterogeneity (42). The cystic or hemorrhagic components can give the so-called “bowl of grapes” appearance (42). Fluid-fluid levels are seen. These tumors tend to displace muscle, tendons, or ligaments (42,44). As with CT, the solid components of the synovial sarcoma will enhance with contrast (42).

Absence of calcification, presence of hemorrhage and cystic components, fluid levels, marked heterogeneity, and early, arterial phase enhancement, all speak to high-grade lesions (45) and portend a poorer prognosis. Lesions that occur in older patients or that are greater than 5 cm in size also carry a worse prognosis (42).

Although the treatment of choice is complete excision, the proximity of these tumors to joints usually precludes this. Wide local excision is more commonly performed with radiation and, more controversially, chemotherapy to treat potentially positive margins. Radiation has been shown to reduce the local recurrence rates that are as high as 50% (46). After treatment, MR images may show edema or necrosis on T2-weighted images. Decrease in size may also be a feature (42).

Neurofibrosarcoma

Neurofibrosarcoma, also termed malignant schwannoma or even more appropriately malignant peripheral nerve sheath tumors, arises from the neural sheath cells and occur more frequently in patients with neurofibromatosis type I and after radiation exposure (47–49). Five to thirteen percent of patients with neurofibromatosis I will develop a neurosarcoma (50). Neurofibrosarcomas represent less than 1% of soft tissue tumors and only 5% to 10% of sarcomas (51,52). In addition to the more common malignant schwannoma, other types, including glandular malignant schwannoma, malignant epithelioid schwannoma, and malignant Triton schwannoma, have

been described. In the Triton type, features of rhabdomyosarcoma may coexist with the malignant neural tumor (53). Clinically, they grow rapidly and present with pain or neurologic deficit. The Brachial plexus is a common site (51). Small tumor size, surgical resectability, and the use of postoperative radiation, all contribute to a better prognosis. Both local recurrence and metastases, especially pulmonary, are frequent occurrences and have a much poorer survival associated with them (49).

Imaging of neurofibrosarcomas is characterized by contrast enhancement with areas of necrosis and fibrosis. The lesions are usually well defined, often ovoid masses, but may also be plexiform growing along the nerves. On T1-weighted and T-2 weighted MR images they will be heterogeneous. Small, high-signal foci on T-2 weighted MR images is likely consistent with necrosis. On CT, an iso- or hypodense lesion will be seen. With contrast enhancement, low attenuation will be seen that represents necrosis. Spiculated periosteal bone reaction may be present in adjacent bone. Any bone erosion can be defined on CT (53).

The management approach includes biopsy, staging, and then a surgical approach to therapy. While local resection is sometimes possible, there is often a risk of neural or vascular interruption with significant loss of function. Amputation may be necessary, although limb-sparing approaches with wide resection and brachytherapy are becoming more common. External beam radiation therapy may also be used postoperatively with variable results (47,49). The role of adjuvant chemotherapy is less certain (49).

Leiomyosarcoma

Although leiomyosarcoma can arise in smooth muscle anywhere in the body and are more frequently associated with viscera, especially the uterus, bladder, and hollow viscera, a significant portion occur in the extremities (4), most commonly arising from vascular smooth muscle (54). Like other soft tissue sarcomas, prior radiation, chemotherapy, or genetic predisposition may promote their occurrence (55). The vast majority of leiomyosarcomas are high grade (56). Larger size, older age, tumor depth, high tumor grade, and presence of necrosis all carry a worse prognosis (54,56). Metastasis occurs somewhat more often than local recurrence (56).

On MR images, these tumors tend to be homogeneous and ovoid, showing enhancement with gadolinium. On T1-weighted imaging, they have low signal intensity and on T2-weighted imaging, moderately high signal intensity (57,58). When associated with larger vessels, there may be an intravascular component. On CT, these tend to be heterogeneously enhancing masses.

Biopsy for diagnosis that risks disruption of the tumor is a major risk factor for metastasis (54). Thus, wide surgical excision of these tumors, that are generally well circumscribed, is preferred with subsequent adjuvant radiotherapy and, occasionally, chemotherapy (54,59). Adequate local therapy is important for good outcome (56).

Clear Cell Sarcoma

Clear cell sarcomas are also called malignant melanoma of soft parts. Histologically, these tumors have melanocytic features and can be distinguished from melanoma only by cytogenetics (60). They occur primarily in the lower extremities and tend to be in relation to tendons, fascia, or aponeuroses, and present clinically as slowly enlarging, painless soft tissue masses (61). Their pattern is invasive and the overlying skin and subcutaneous tissue may show changes. Lymph node metastases are common at presentation, and sentinel lymph node biopsy should be part of the initial surgical management (60). They tend to recur locally after surgery (61). Larger tumors carry a worse prognosis (62) with greater risk for metastasis to lung, liver, heart, and bone (60).

On MR images, these tumors will be well defined and hypointense, isointense, or even slightly hyperintense on T1-weighted imaging relative to muscle. When they are hyperintense on T1-weighted imaging, they will show melanocytic differentiation immunohistochemically (63). They may be hyperintense on T2-weighted imaging and will enhance intensely and homogeneously with gadolinium (60,63). Occasionally, these tumors may show necrosis and there may be associated destruction of bone (63).

Clinically, these tumors should be managed aggressively with surgery (62). While the role for radiation therapy or chemotherapy is somewhat controversial (60), some authors suggest that adjuvant radiation therapy may have a beneficial role and that doxorubicin-based chemotherapy may reduce the incidence of recurrence (61).

Fibrosarcoma

Although MFH was once lumped in to the category of fibrosarcoma, the term “fibrosarcoma” is now reserved for tumors arising from fibroblastic stroma with atypia (4). It is the second most common sarcoma in children after rhabdomyosarcoma and the most common in children less than one year of age, so called “infantile fibrosarcoma” (64). A second peak occurs in adolescence, the adult type. Infantile fibrosarcoma presents clinically as a rapidly enlarging, painless mass with reddening of the skin over the mass. Ulceration may occur. In the adult type, the

growth rate is slower in these painless masses (64). For infantile fibrosarcoma, survival is high in the 80% range with a lower rate of metastases (65). In the adult type, local recurrence is often followed by metastasis with lung being the most common site.

MRI of infantile fibrosarcoma will show a large, heterogeneous mass likely reflecting necrosis with hypointensity on T1-weighted imaging and hyperintensity on T2-weighted images (66). On CT, these tumors will be hypodense relative to muscle (66). In adult-type fibrosarcoma, the MRI appearance is nonspecific. CT may be useful for identifying bone erosion, calcification, or ossification (66). It is also useful for assessing metastatic disease, particularly in the lung (65).

Management entails surgical excision with a very limited role for adjuvant radiation therapy or chemotherapy, although the infantile type may be slightly more chemosensitive (64,65). Neoadjuvant therapy has yielded some durable responses, possibly because it can reduce the tumor to one that is surgically manageable (64,65).

Rhabdomyosarcoma

Among infants and children, rhabdomyosarcoma is the most common soft tissue tumor and represents 4% of all tumors at this age (67). Rhabdomyosarcomas may occur as second primary malignancies in a previously irradiated field (68). Of the two subtypes, alveolar has a greater tendency to metastasize than embryonal (69) and has a higher rate of relapse. It is more common among the extremity rhabdomyosarcomas (69). As with many sarcomas, lung is the most frequent site of metastasis (67). Alveolar subtypes are also associated with a worse five-year survival. More advanced stage at presentation is also associated with lower survival rates (69). Staging should include evaluation of regional lymph node involvement as well as distant metastasis (67).

Unenhanced CT will show a low density, ovoid mass, usually within a muscle. With contrast either on CT or MRI, slight to marked heterogeneous enhancement may be seen, but not uniformly. Frequently, the appearance on both T1- and T2-weighted MR images is nonspecific (68,70). On T2-weighted imaging, the tumors tend to be high signal and isointense to slightly increased signal on T1-weighted imaging (70). Fluid-fluid levels have been described, although hemorrhage and necrosis are not common features of rhabdomyosarcomas (68,70).

Treatment includes resection when possible, chemotherapy with or without radiotherapy, followed by second look surgery and then salvage chemotherapy for those without complete response (69,71). Radiotherapy is usually reserved for later stage disease or those with microscopic residual disease after resection (71).

Epithelioid Sarcomas

Epithelioid sarcomas have a predilection for the upper extremity, but are rare. Although their peak age incidence is 10 to 35 years, they have been observed from infancy through advanced age (72). They have a somewhat better outcome in females in whom epithelioid sarcoma tends to occur at a younger age (73). They may present with ulceration of the skin and may be subcutaneous in location (4). Their clinical presentation may be deceptively benign and they may be confused with rheumatoid nodules, necrotizing granulomata, or even squamous cell cancers (72). However, they show a marked tendency to recur and to metastasize. Poor prognostic factors include proximal extremity location (72), large size, hemorrhage, necrosis, deep location, early recurrence, vascular invasion, and lymph node metastasis (74,75).

Since these tumors sometimes calcify, this may be a feature on CT; and when in proximity to bone, periosteal reaction may be identified on CT (72). They have been reported to appear multilobular on CT (76). On T1-weighted imaging, they are most often isointense to muscle. Heterogeneity on T1-weighted imaging may be due to necrosis. These tumors may have an infiltrative appearance, may occur in muscle or in subcutaneous tissue. On T2-weighted imaging, they may appear homogenous with hypointense signal corresponding to calcification, hyperintense, or isointense signal compared with fat. Peritumoral edema is a frequent characteristic. Enhancement is often heterogeneous because of necrosis, but may be homogeneous (72). Regional lymphadenopathy should also be assessed on CT or MRI (76).

Clinical management hinges on an aggressive surgical approach. The role of lymphadenectomy is unclear (73). Residual tumor after surgery is a poor prognostic factor (73). Radiotherapy may be used preoperatively or postoperatively. Combined adjuvant radiotherapy and chemotherapy appear to decrease the incidence of local recurrence, but the evidence is not conclusive (73,77). Still, there is a high incidence of lymph node and lung metastasis (78).

Alveolar Soft Part Sarcomas

Alveolar soft part sarcomas are histologically consistent but distinctive tumors that occur most frequently in the deep soft tissues and, more commonly, in young women. They do occur in both children and adults. In children, they are more common in the orbit and head and neck in general. They may also present as primary tumors of the bone. While they have a relatively indolent course and local control can be achieved, they tend to present with metastases after a prolonged course (79). The most com-

mon sites of metastases are lung, bones, and brain (79). Good prognostic signs include a small size, absence of metastases at presentation, and a younger patient (79–81).

On imaging, they are found to be vascular (79,82) with prominent and tortuous venous structures (83,84). Angiographically, they show delayed washout and arteriovenous shunting (84). On MRI, they have been described as isointense or high intensity on T1-weighted imaging (82–84), and on T2-weighted imaging, they tend to show high-intensity signal with scattered areas of signal void on either type of sequence (83,84).

Optimal clinical management includes wide and adequate resection of the primary. Adjuvant radiation therapy improves local control, but chemotherapy has not been effective in that setting (79,81). The role of either treatment modality remains questionable (85). When primary tumors are not completely resectable, some success has been described with neoadjuvant chemotherapy for alveolar soft part sarcomas (86). DCE-MRI has been useful for following response to therapies (82). For metastatic disease to the lungs, resection in pediatric patients has been advocated to improve survival (85,87). Intensive chemotherapy in the metastatic setting does show some efficacy (88), and when chemotherapy has failed to elicit a tumor response, interferon-alpha-2b has yielded responses (89).

Vascular Sarcomas

These sarcomas all arise from blood vessels and the subtypes include epithelioid hemangioendothelioma, Kaposi sarcoma (KS), and angiosarcoma. Epithelioid hemangioendothelioma is relatively less aggressive, although not uniformly so (90), unlikely to metastasize, and usually arises from a venous structure. Angiosarcoma may arise in the heart (91), the head and neck (92), liver (93), in tissue such as the breast, which has been previously irradiated (94,95), or in lymphedematous subcutaneous soft tissue (96).

Angiosarcoma

Angiosarcomas constitute about 4% of soft tissue sarcomas in one series (97), are prone to hemorrhage (98), and when metastatic to the lungs may present with hemoptysis (93). A majority of patients have metastases at initial presentation (91). For angiosarcoma, size is the most important prognostic factor (99). While prognosis for many soft tissue tumors can be evaluated by histologic grading, this is not useful for prognostication in angiosarcomas and epithelioid angiosarcomas (100).

On ultrasonography, these are ovoid, solid, and hyperechoic (101). On CT, unenhanced lesions may be hypoattenuating in sites of old hemorrhage and hyperattenuating in sites of fresh hemorrhage (102). With contrast, lesions

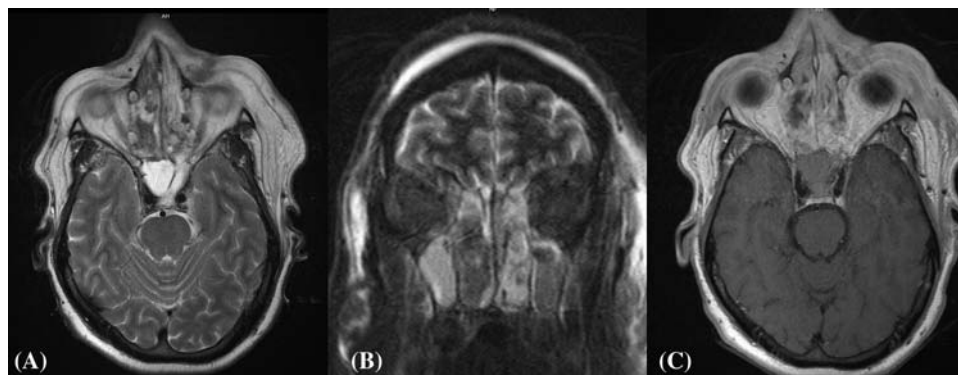


Figure 3 MRI of angiosarcoma. A 57-year-old man with a newly diagnosed angiosarcoma filling the right nasal cavity. (A) Axial T2-weighted MR image at the same level shows relatively low signal lesion in the posterior aspect of the nasal cavity just anterior to the high signal mucocoele in the sella. (B) Coronal STIR image shows low signal soft tissue mass, which fills the right nasal cavity adjacent to the right fluid-filled maxillary sinus. (C) Axial T1-weighted MR image with contrast through the level of the tumor shows heterogeneous enhancement of the right nasal cavity with viable tumor at its periphery and central necrosis.

may only partly enhance, more commonly at the periphery or heterogeneously (103). In subcutaneous lesions, T1-weighted MRI will show thickened subcutaneous fat with a reticular pattern of hypointensity. T2-weighted imaging with fat saturation or contrast enhanced T1-weighted imaging may better demonstrate muscle invasion (104). On DCE-MRI, angiosarcomas will be lobular and will enhance rapidly, intensely, and heterogeneously (101). Vascular channels with slow-flowing blood at the periphery of these lesions may cause hyperintensity on T2-weighted imaging (Fig. 3) (105). On the other hand, in the angiosarcoma that arises in the setting of lymphedema, the lesion may show hypointensity on T2-weighted and STIR images (106). On MRI when there is bone involvement, a fluid-fluid level is occasionally seen (107). PET/CT for cutaneous angiosarcoma has not only been useful in demonstrating intense metabolic activity (Fig. 4), but may also show periosteal reaction in the adjacent bone on the CT images (108).

Treatment of angiosarcoma as with other soft tissue sarcomas depends on good local control with surgical resection and adjuvant radiotherapy alone, or in combination with interferon (99,109). Treatment of recurrence or metastatic disease relies on chemotherapy usually antiangiogenic (110).

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma is a much less aggressive sarcoma. However, it may spread systemically to involve bone, liver, and spleen (90). When it does involve the bone, its appearance on MRI is that of a solid lesion (111). On CT, the lesions of bone are lytic (111). In the liver the lesions are usually multiple with a central low density owing to the characteristic central necrosis. Typically, they are found at the periphery of the liver with extension

to and retraction of the liver capsule (103). On PET, lesions in the lung have shown increased uptake (112).

The first approach to treatment of these lesions is wide surgical excision (111) and sometimes accompanied by lymph node dissections. This is usually sufficient to achieve both local control and long-term survival (113–115). Adjuvant radiotherapy may be used (116). In extensive liver involvement, liver transplantation has achieved prolonged disease-free intervals (113).

Kaposi Sarcoma

KS occurs in a sporadic form usually in males of Jewish, eastern European, or Mediterranean descent (117) and, in an endemic form, in males in the fourth decade predominantly in East and Central Africa. These forms of KS tend to be indolent and primarily a disease of the skin. The endemic form may be locally invasive involving adjacent bone. In addition, a more aggressive form of endemic KS has been identified in children. The sporadic form may spread to visceral organs, but this occurs in less than 20% of patients (117). KS also has been associated more recently with immune suppression either in the setting of AIDS or in patients on chronic immunosuppression for organ transplant (so-called iatrogenic KS) (118). Iatrogenic KS has been described in lungs (119) and also in the allograft itself (120–122). AIDS-related KS is a more virulent disease but has decreased in incidence with the introduction of antiretroviral therapy and in the setting of highly active antiretroviral therapy (HAART) is much less aggressive in its behavior (118,123). Skin, mucosa, and visceral involvement are all common in its more aggressive form.

Radiographically, the cutaneous lesions will manifest as skin thickening. The lymph nodes tend to be hypoattenuating on CT relative to muscle (Fig. 5) and there may be

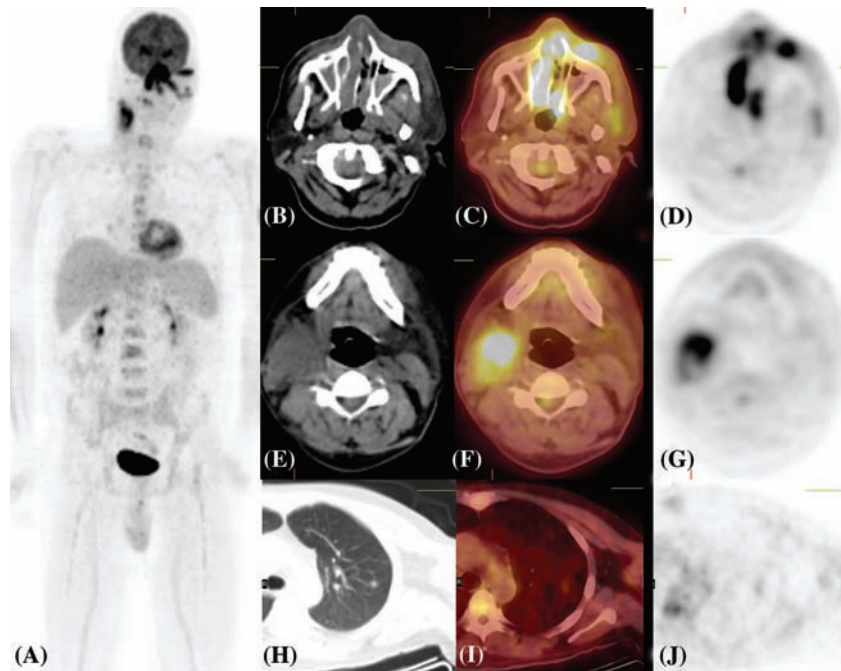


Figure 4 Same patient as Figure 3. (A) Anterior view from a maximum intensity projection of the whole-body PET shows uptake in the nasopharynx and the right neck. (B) Axial CT acquired as part of the PET/CT shows a soft tissue mass filling the right nasal cavity and in the posterior left nasal cavity, soft tissue prominence over the left cheek, and opacification of the right maxillary sinus. An air fluid level is seen in the left maxillary sinus. (C) The fused PET/CT image shows that there is increased metabolic activity associated with the soft tissue mass in the right nasal cavity and posterior left nasal cavity. Subcutaneous activity corresponds to the soft tissue prominence of the left cheek on CT. (D) The FDG PET slice at this level shows the location of the metabolic activity. (E) CT, (F) fused image, and (G) PET show the enlarged lymph node with a necrotic hypometabolic area in the posterior triangle. Finally, (H) CT with lung windows, (I) corresponding fused image, and (J) FDG PET show faint uptake in a very small pulmonary nodule consistent with a metastasis.

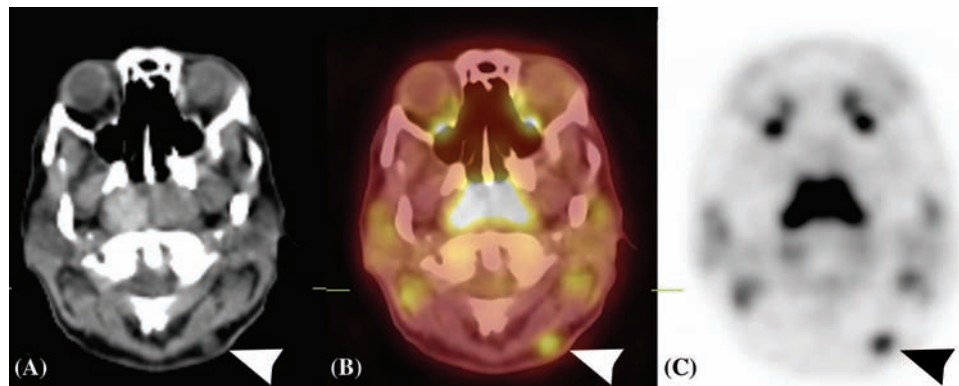


Figure 5 A 37-year-old HIV-positive man with decreasing T-cell count. He presented with lymphadenopathy and skin lesions typical of KS. A palpable subcutaneous nodule (arrowhead) is seen as somewhat low attenuation relative to muscle in the right posterior lower scalp on (A) CT and demonstrates increased metabolic activity on the (B) fused, and (C) FDG PET study. In addition, metabolically active bilateral cervical lymph nodes are present. Biopsy of one node was positive for KS but another node showed only evidence of HIV-associated lymphadenopathy. *Abbreviation:* KS, Kaposi sarcoma.

accompanying changes of lymphedema in the subcutaneous tissues as well. Visceral lesion may be infiltrative or nodular and will enhance with IV contrast (118). Lung involvement may present with ill-defined nodules, lym-

phadenopathy, or pleural effusions (119). Multiple pulmonary nodules may distribute along the bronchovascular bundles and coalesce (118). On MRI, KS masses will show increased signal on T1-weighted images, decreased

signal on T2-weighted images, and contrast enhancement with intravenous gadolinium (124). Hepatic lesions will be hypoattenuating and will remain so immediately after contrast administration. More delayed images may show increasing attenuation in hepatic lesions over time (118). In the bones, KS will be lytic on CT and may not be obvious on T1-weighted MRI, but will show intense enhancement after gadolinium administration. These lesions are active on conventional bone scintigraphy as well (118).

In the HIV-positive patient or the patient with a transplant, treatment of KS is aimed at reversing or modifying the immunosuppression (125–127). In AIDS-related KS, HAART plays a role in reversing the disease along with cytotoxic agents. Local chemotherapy, including retinoids or vinblastine for less extensive lesions may be used. Cryotherapy and laser treatments have some efficacy. Radiotherapy may be used with bulkier lesions (128). In addition, antiangiogenic agents and rapamycin have shown promise (128,129). Systemic chemotherapy is reserved for more advanced disease. First-line drugs include taxanes and liposomal anthracyclines, but other agents including vinblastine and bleomycin have been tried (128). Interferon-alpha also has been used with responses requiring long periods of therapy (128). For classic and endemic KS, radiotherapy and systemic chemotherapy, including taxanes (130,131), are reserved for symptomatic and aggressive lesions. Surgery may be the more usual first-line approach taken (131).

THE ROLE OF FDG PET/CT IN EVALUATING SOFT TISSUE SARCOMA

FDG PET and now FDG PET/CT can make significant contributions to identification of the primary, staging, prognostic assessment, monitoring, and assessment of treatment efficacy in soft tissue sarcomas (5,132). In addition, when children present with metastatic disease from an unknown primary PET/CT has been found to be

helpful in identifying the site of sarcoma (133). Although uptake in a sarcoma is not always florid on PET, the current standard for positivity is uptake greater than that of the corresponding contralateral soft tissue (5). Co-registered CT helps to identify faint uptake in either very small structures or metabolically indolent tumors (67).

Grading of Tumors and Prognosis

A meta-analysis of grading of soft tissue sarcomas by metabolic PET that included many types of soft tissue sarcomas showed that SUVs of histologically low-grade soft tissue sarcomas were not significantly different from those of high-grade tumors. Nonetheless, GLUT-1 expression and SUVs were shown to correlate with immunohistochemical markers of proliferation like MIB-1 and mitotic indices as well as with p53 overexpression (134). Metabolic rate as assessed by FDG PET has been shown to correlate with tumor grade to a significant extent (135). A number of authors have suggested that FDG uptake correlates with tumor grade (Fig. 6) (135–139). For example, the histologic grade of liposarcomas does tend to correlate with intensity of uptake (136). Therefore, the use of FDG PET in a metabolically heterogeneous tumor is important for directing tumor biopsy to sample the region of the tumor that will demonstrate the most aggressive features (Fig. 1) (1,18,135).

More importantly, metabolic activity as measured by FDG PET and SUV appears to carry prognostic significance. While tumor grade generally has prognostic significance, this has not been entirely reliable for predicting prognosis (135). In a large, but retrospective series, Eary et al. (140) have shown a statistically significant correlation between overall survival and SUVmax at diagnosis, to a greater degree even than that between tumor grade and overall survival. In that study, a doubling of SUVmax was associated with a 60% increase in the risk of death (140). Schwarzbach et al. showed 84% overall survival in

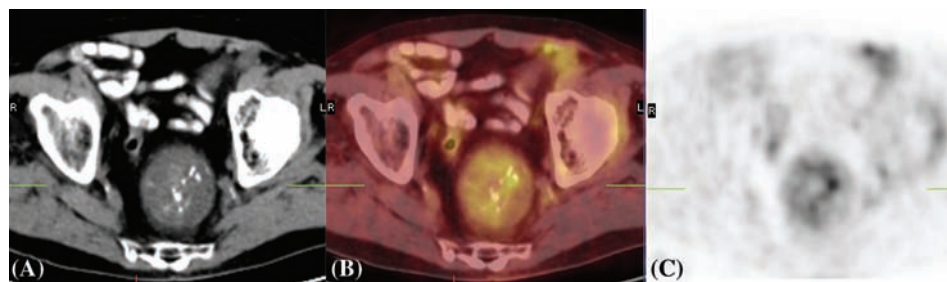


Figure 6 An 83-year-old man with a newly discovered pelvic mass demonstrating calcification and heterogeneity on (A) CT with only one focus of relatively intense metabolic activity (SUV 2.8) on (B) corresponding fused and (C) FDG PET images. On biopsy this was a low-grade sarcoma.

a group of patients with resectable soft tissue sarcomas, if the SUV preoperatively was less than 1.59, 45% for an SUV between 1.59 and 3.6, and 38% for SUV greater than 3.6 (141). They also showed a difference in five-year local or distant recurrence-free survivals in relation to SUV: 66% for primary tumors with SUV less than 1.59, 24% for SUV greater than 1.59 and less than 3.6, and 11% for SUV greater than 3.6 (141). There was a relationship between tumor grade and SUV in these patients, but tumor grade was still the strongest predictor of disease-free survival in that group of patients (141). In patients with neurofibromatosis-1, the SUV of malignant peripheral nerve sheath tumors correlated with grade and predicted long-term survival better than tumor grade (142). In a series of patients with high-grade sarcoma, SUVmax of greater than 6 correlated with an increased risk of developing recurrence and metastasis (143). Statistical modeling that incorporates the heterogeneity and the intensity of uptake on FDG PET (SUVmax) as well as the characteristics of the tumor boundary on imaging has also been used to provide prognostic information on survival (144).

Staging and Identification of Primary and Metastatic Tumors

PET/CT has been helpful in assessing the local extent of sarcomas adding information even to MRI, especially in confirming tumor compared rather than tissue reaction (108). Furthermore, FDG PET/CT plays a role in establishing the presence of distant metastases and also in assessing regional lymph-node involvement, an area where clinical staging often misses disease (145,146). In the meta-analysis by Bastiaaet et al. (2), FDG PET (alone) had a sensitivity of 88% and a specificity of 86%. Low grade and small sarcomatous lesions accounted for the compromised sensitivity (2).

In lung metastases, slightly less than 1 cm may be the limits of detection on PET alone (147). PET/CT shows increased sensitivity over PET for pulmonary metastases because the CT from the study increases the sensitivity from 66.7% for PET alone to 90% for the accompanying CT alone (148). Dedicated chest CT in a different group of patients showed a sensitivity of 96.8% in this series. Specificity for PET was 98.4%, with a specificity of 87.5% for CT obtained at PET/CT and of 93.9% for dedicated chest CT (148). While the differences between the two types of CT may not have been significant, the trend speaks to the CT image quality and resulting resolution. The better performance of CT for lung metastases in soft tissue sarcomas has been confirmed by other groups as well (149).

Nonetheless, the utility of PET and PET/CT for staging has been documented for assessing lymph nodes in children

presenting with alveolar rhabdomyosarcoma, where FDG uptake identified small, and mild-to-moderate metabolically active draining lymph nodes subsequently found to be histologically involved (67). Especially in those cases where both lymph node size is normal and intensity of FDG uptake is equivocal, PET/CT can provide a guide to biopsy (67). It is likely that the high metabolic activity of rhabdomyosarcoma, a high-grade sarcoma, results in an increased sensitivity of FDG PET for very small lymph node metastases (146). False-positive lymph nodes have been reported as well in rhabdomyosarcoma (150). In children, PET/CT has been useful in diagnosing metastatic involvement in bones and soft tissue not suspected by physical exam or by conventional imaging procedures including MRI, bone scintigraphy, and chest CT (133,150). In fact, in one series, PET/CT was the only modality to detect distant metastases in some patients (150). In another series of 19 patients, PET influenced a change therapeutic approach in 13% patients and was otherwise helpful to therapy planning in 80% of the patients scanned (151).

Monitoring for Recurrence

Early detection of recurrence is key to improving outcome (150). In general, patients are followed closely for three to five years for possible recurrence (133). Monitoring for suspected recurrence with FDG PET/CT adds specificity to conventional imaging procedures in patients with rhabdomyosarcoma (146) and sensitivity for unusual sites of recurrent rhabdomyosarcoma (133). In a small series of pediatric patients with various soft tissue sarcomas, PET/CT demonstrated excellent accuracy in diagnosing local relapse and for metastases to lymph nodes and bone marrow (150). The lung was the only site where PET/CT showed decreased sensitivity compared with conventional modalities (150,151).

As in initial therapeutic planning, FDG PET may identify disease or disease extent that will change subsequent management (Fig. 2) (151). For example, when patients present with new and potentially resectable lung metastases, FDG PET will provide important information concerning other sites of disease (152). Extrapulmonary metastases have been reported in 20% of patients with solitary metastatic soft tissue sarcoma to lung (152).

Tumor Response

While MRI and CT have been the primary modality for assessing tumor response following chemotherapy or radiation, it is well accepted that morphologic change may be minimal or delayed in responding treated tumors (133). PET/CT has been useful in assessing the completeness of tumor resection and the response of tumors

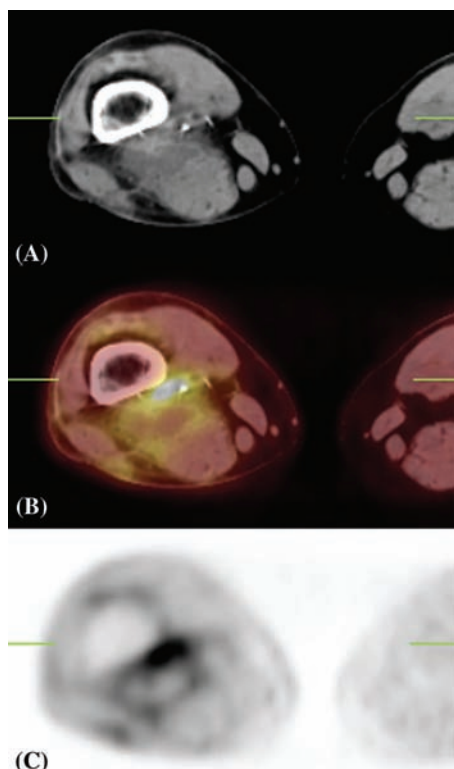


Figure 7 A 45-year-old man with a history of a recurrent sarcoma treated with chemotherapy. This PET/CT was obtained after completion of chemotherapy. There is persistent abnormality on (A) the CT and (B) fused, and (C) FDG PET images show residual activity at the recurrence site consistent with residual tumor.

to chemotherapy, external beam radiation, and even radiosurgery (Fig. 7) (59,133). A significant decrease in SUV in tumors treated with either chemotherapy or radiation therapy is associated with a prolonged relapse-free survival; conversely, persistent uptake portends early recurrence (153). In patients undergoing isolated limb perfusion with interferon, a decrease in SUVmax of greater than 75% at two weeks and eight weeks after therapy was associated with a complete histologic response (10). In the neoadjuvant setting, FDG PET provides an indication of chemosensitivity, and by extension, prognosis (146). In high-grade sarcomas treated with neoadjuvant chemotherapy followed by complete resection and adjuvant radiation, a greater than 40% decrease in SUV after completion of neoadjuvant therapy was associated with a significantly lower risk of recurrence and death (143). False FDG positive uptake in treated tumors has been reported in posttherapy inflammation (10). This may explain the variable results of FDG PET two months after radiosurgery, compared with more reliable results at six months after radiosurgery (59).

SUMMARY

Soft tissue sarcomas are diverse group of tumors whose grade and metabolic activity as assessed by FDG PET are important predictors of prognosis. Accurate assessment of the extent of the primary and its resectability is crucial to the effective management of soft tissue sarcomas since for most soft tissue sarcoma, complete surgical resection provides the best outcome. MRI has been the main modality for assessing primary soft tissue sarcomas because of the important anatomic data provided. Chest CT, usually dedicated CT rather than as part of PET/CT, provides the best assessment for lung metastases. However, increasingly, the role of PET and PET/CT, primarily with FDG, has been appreciated in identifying nodal and distant metastases, diagnosing local and distant recurrence and in determining response to therapy.

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PET/CT Imaging of Cutaneous Malignancies

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PET/CT OF CUTANEOUS MALIGNANCIES

A rationale for the use of positron emission tomography (PET) in the evaluation of cutaneous malignancies was formulated in 1991 when Wahl and Kern, in separate studies, demonstrated that murine melanomas and human melanoma xenografts preferentially concentrated radio-labeled glucose analogs (1,2). Gritters and colleagues shortly thereafter demonstrated that glucose labeled with radioactive fluorine-18 in the form of fluorodeoxyglucose (FDG) imaged melanoma metastases with high sensitivity and specificity (3). Additional studies confirmed these initial impressions and in 1999, Medicare approved coverage of FDG PET for evaluation of recurrent melanoma. In 2001, coverage was expanded to include initial diagnosis, staging, and restaging of melanoma. The only clinical scenario in which melanoma is not covered is for staging of regional lymph nodes (4).

Most of the research evaluating the utility of PET and PET/computed tomography (CT) for cutaneous malignancies has remained limited to the study of melanoma, not surprisingly, because of its prevalence and the high mortality rate for those with metastatic disease. More recently, new data has emerged demonstrating that PET has potential utility for patients with other types of cutaneous malignancies. In particular, Merkel cell carcinoma (MCC), a malignant neuroendocrine tumor of the skin, has been examined,

and preliminary findings suggest a role for PET/CT in the management of these patients. New data has also become available regarding the performance of PET in cutaneous squamous cell carcinoma (CSCC) and basal cell carcinoma (BCC), and a more expansive review of the use of PET and PET/CT in cutaneous malignancies is now possible. This chapter aims at summarizing the current literature concerning the use of PET/CT for all cutaneous malignancies. A review of the CT appearance of melanoma and MCC will be included to supplement a full discussion of PET and PET/CT.

PET/CT IN MELANOMA

Introduction

The American Cancer Society estimated that in 2007 there would be 59,940 new cases and 8,110 deaths in the United States from cutaneous melanoma. Approximately 83% of patients with localized melanoma are cured by surgery and 98% of these individuals are alive at five years following their diagnosis. Unfortunately, the prognosis for patients who harbor metastatic disease is poor. Five-year survival is 64% for patients with regional metastases and 16% for those with distant metastases (5). Table 1 lists the current American Joint Committee on Cancer staging system for melanoma.

Table 1 2001 AJCC Melanoma Staging System

Stage Ia	Primary nonulcerated tumor <1.0 mm
Stage Ib	Primary nonulcerated tumor 1.01–2.0 mm or primary ulcerated tumor <1.0 mm
Stage IIa	Primary nonulcerated tumor 2.01–4.0 mm or primary ulcerated tumor 1.01–2.0 mm
Stage IIb	Primary nonulcerated tumor >4.0 mm or primary ulcerated tumor 2.01–4.0 mm
Stage IIc	Primary ulcerated tumor >4.0 mm
Stage IIIa	Primary nonulcerated tumor any thickness and 1–3 micrometastatic lymph nodes
Stage IIIb	Primary nonulcerated tumor any thickness and 1–3 macrometastatic lymph nodes
	Primary ulcerated tumor any thickness and 1–3 micrometastatic lymph nodes
	Any primary tumor and in transit or satellite metastases
Stage IIIc	Any primary ulcerated tumor and 1–3 macrometastatic lymph nodes
	Any primary tumor and 4 or more metastatic nodes
	Matted nodes
	In transit or satellite metastases with any metastatic nodes
Stage IV	Any distant metastases

Source: From Ref. 74.

Given the dramatic differences in survival rates among patients with varying stages of the disease, it becomes important to accurately stage patients at initial diagnosis and during follow-up. Estimation of the extent of disease is critical for planning appropriate therapy, selecting individuals for clinical trials, and providing realistic estimations of prognosis. This chapter will briefly outline the conventional techniques employed in the staging of patients with melanoma with a discussion of their benefits and limitations. A thorough discussion of how PET and PET/CT may overcome some of the limitations will then follow.

Diagnosis and Conventional Management

Once a melanoma has been diagnosed by biopsy of a suspicious cutaneous lesion, further management depends on the thickness of the primary tumor and the presence or lack of clinical signs of metastatic disease. Virtually all patients undergo a wide local excision to ensure complete removal of the primary tumor. For patients with lesions less than 1 mm in thickness, the risk for metastases is generally considered low, and no further management is necessary. For individuals with lesions greater than or equal to 1 mm, or with a Clark level greater than or equal to IV (deep dermal or subcutaneous fat invasion), a sentinel lymph node biopsy is typically performed (6). Histologic evaluation of the sentinel lymph node, preferably using thin cuts through the entire node (7), is very useful for determining prognosis and is employed to select patients that will benefit from a complete regional lymph node dissection (8).

Traditionally, patients first diagnosed with melanoma have been screened using chest radiography and serum LDH measurements in an attempt to look for occult

metastatic disease. In some cases, patients have been screened with MRI or CT. Unfortunately, recent studies have demonstrated a low sensitivity and specificity for these modalities (9–11), and consequently the National Comprehensive Cancer Network and others recommend against these studies in patients with no evidence of local or distant metastatic disease.

Conventional follow-up for melanoma includes routine skin exams for patients with in situ melanoma, and a skin and lymph node exam every 3 to 12 months for patients with less than 1 mm local disease. For patients with more advanced primary tumors or known or suspected metastases, more extensive hematologic testing and CT imaging may be useful during follow-up (12). PET/CT is now playing a greater role in the follow-up of patients with melanoma and will be discussed in detail below.

CT in Melanoma

The CT appearance of melanoma was described in numerous reports throughout the 1980s (13–22) and summarized in detail by Fishman and colleagues in 1990 (23).

Shirikhoda and colleagues reported on the frequency of melanoma metastases at various sites on CT. Common locations included the head and neck (Fig. 1), eye (Fig. 2), and genitourinary system (79%, 77%, and 67% of patients, respectively) (14). Silverman and Shirikhoda reported the prevalence of hepatic metastases to be 17% to 23% and splenic metastases to be 1% to 5% (Fig. 3) (14,15). Metastases to the mesentery or bowel are also common and can occur in at least 8% of patients (14). Renal metastases have been described in autopsy series in 35% of patients (24) and adrenal metastases have been noted in up to 50% of patients at autopsy (25). All of these

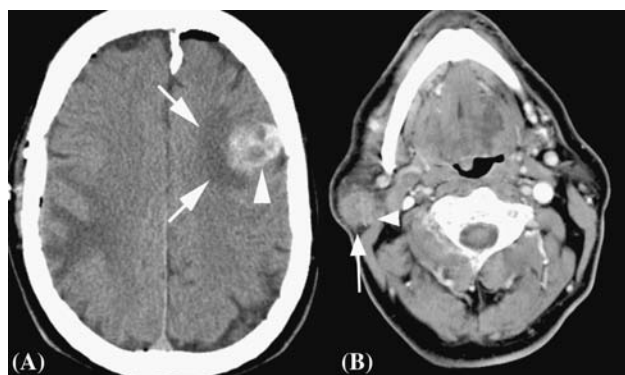


Figure 1 (A) Melanoma brain metastasis. IV contrast-enhanced CT demonstrates an enhancing mass (*arrowhead*) surrounded by reactive edema (*arrows*). (B) Metastasis to the right parotid gland. A 61-year-old male with a history of right shoulder melanoma with right supraclavicular nodal metastases presented with new swelling below the right ear. IV contrast-enhanced CT demonstrates a 2×2 cm enhancing intraparotid metastasis (*arrow*) with possible invasion of the anterior edge of sternocleidomastoid muscle (*arrowhead*).



Figure 2 A 65-year-old female with diffuse supratentorial metastases of melanoma. Noncontrast CT of the head demonstrates a 1.4×1.3 cm intraorbital metastasis (*arrowhead*) associated with the medial rectus muscle.

lesions are potentially detectable by CT. Although reportedly less common, melanoma can also involve bone and muscle (Figs. 4,5).

Subcutaneous metastases can occur near the primary tumor in the form of satellite or in-transit metastases, and distant subcutaneous lesions can occur as the result of hematogenous dissemination of tumor (Fig. 6). Lymph node metastases are also common, particularly within the local lymph node basins draining the location of the primary tumor. Finally, lung metastases (Fig. 7) are common and are seen at autopsy in up to 70% of individuals (25).



Figure 3 Melanoma metastases in the liver and spleen. Portal-venous phase contrast enhanced CT demonstrates numerous round and ovoid hypodense lesions (*arrows*), some of which demonstrate very mild peripheral enhancement (*arrowhead*).

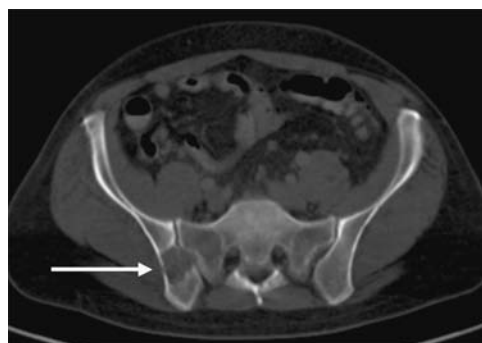


Figure 4 Metastatic melanoma to the right iliac bone. IV contrast-enhanced CT demonstrates a lytic mass with irregular borders (*arrow*).



Figure 5 A 52-year-old male with diffusely metastatic melanoma. IV contrast-enhanced CT demonstrates a heterogeneously enhancing right piriformis muscle metastasis (*arrow*).

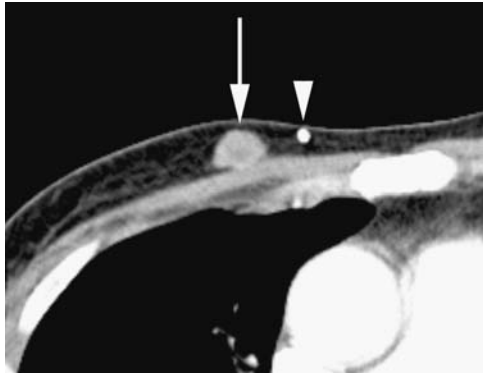


Figure 6 A 45-year-old male with metastatic melanoma. IV contrast-enhanced CT demonstrates a subcutaneous metastasis in the right anterior chest wall with mild peripheral enhancement (*arrow*). Note also chemotherapy port tubing (*arrowhead*).



Figure 7 Pulmonary melanoma metastases. CT lung window demonstrates numerous round and ovoid lesions that vary in size, some of which are slightly lobulated.

Fishman and colleagues described the myriad appearance of melanoma metastases on CT. Hepatic metastases (Fig. 3) were reported to vary in appearance and can be single or multiple, necrotic or calcified, and sometimes hypervascular. Metastases to bowel were reported to be at times “indistinguishable from that of primary or metastatic adenocarcinoma, lymphoma, or other metastases” and can be infiltrating, ulcerated, single, or multifocal. Some lesions can cause intussusception and other patients will present with bowel wall implants or carcinomatosis (Fig. 8). Renal lesions were described as single or multiple, varying in size, and solid or cystic (often with mural nodules). Adrenal lesions were described as round or oblong. Fishman further elaborated the appearance of bone metastases as “lytic lesions, with or without an associated soft tissue mass.” Continuing with the theme



Figure 8 Peritoneal carcinomatosis due to metastatic melanoma. Contrast-enhanced CT coronal reconstructions demonstrate mesenteric nodal metastases (*arrows pointing left*) and diffuse peritoneal nodularity in the right lower quadrant due to carcinomatosis (*arrows pointing right*).

of variable appearance, they described lung metastases (Fig. 7) ranging in size from 0.6 to 5 cm, often with feeding vessels or associated mediastinal lymphadenopathy. Lymphadenopathy can be solid or necrotic (Fig. 8) (23).

Challenges in the Staging of Melanoma

Despite the advances in patient care associated with the advent of the sentinel lymph node biopsy for staging regional nodes and CT for evaluation of distant metastases, staging of melanoma remained far from perfect. Although useful for identifying which patients should undergo a complete regional lymph node dissection, the sentinel node technique does not determine if a patient has distant metastases that would dramatically alter management. Despite the high spatial resolution of CT, it too has remained limited for the detection of small lymph node metastases and early pulmonary, liver, or other metastases in which lesions are either too small to see or are nonspecific in appearance. There has been a need for a more specific technique to identify early but significant local and distant metastases. The tools of molecular imaging were a fertile ground for such advancements. As will be discussed below, PET and then PET/CT proved to be the next step in advancing the field of melanoma detection.

PET/CT Imaging of Melanoma

Initial diagnosis

There are anecdotal reports of PET and PET/CT detection of occult primary cutaneous melanoma, but no systematic studies of diagnostic accuracy have been performed for detection of primary tumors. There are also a few reports of incidental detection of occult vaginal and gastrointestinal melanomas (26,27). However, the general consensus among experts is that PET/CT in its current form will not likely ever be employed as a screening tool to detect primary tumors. Since when these tumors are in their most curable stage, they are typically below the resolution of current scanners (~5–6 mm).

Initial staging of clinically localized disease

Accurate staging at initial diagnosis of melanoma is crucial to guide appropriate therapy and also to provide important prognostic information to the patient and physician. The presence or lack of local satellite (2 cm or less from the primary lesion) or in-transit (>2 cm from the primary lesion) metastases, local or distant lymph node metastases, or distant extranodal metastases can dramatically alter treatment plans that are designed to maximize benefit and minimize morbidity.

One of the most important prognostic indicators in newly diagnosed melanoma is the presence or lack of metastases in the first lymph node draining the skin at the site of the primary tumor (the sentinel lymph node) (28). Individuals with primary tumors with a thickness of 1 mm or greater are at increased risk for metastases, and accurate noninvasive staging of the sentinel lymph node by

surgical biopsy is useful. In theory, a noninvasive way to evaluate this node and other regional lymph nodes would be beneficial and could spare the patient from invasive procedures.

Initial studies of FDG PET alone for the detection of metastases were not focused specifically on staging of regional lymph nodes and generally examined mixed populations of patients with varying states of disease. Preliminary data was promising with sensitivity ranging from 85% to 100% and specificity ranging from 92% to 100% for detection of all types of metastatic disease (29–31). This data prompted investigators to examine the utility of PET for regional lymph node staging.

Subsequent work performed with better-defined patient populations focusing on individuals with earlier stage disease with no clinical evidence of metastases (more typical for most patients diagnosed with melanoma today) demonstrated much poorer performance for FDG PET and, in particular, for staging of regional nodes. Several more focused studies demonstrated that in patients with newly diagnosed melanoma and no palpable lymph nodes, the sensitivity of FDG PET for detection of local lymph node metastases (sentinel or other) ranged from 0% to 15% with a specificity of 88% to 100% (31–34). The reason for these results is that most early nodal metastases are small and the sensitivity of PET and PET/CT is significantly reduced for lesions smaller than 80 mm³ (35). It is now clear that there is no role for PET or PET/CT in the staging of regional nodes when there are no findings of concern for local or distant metastases (36). Table 2 summarizes the data regarding use of PET for the detection of regional lymph node metastases.

Table 2 Detection of Regional Lymph Node Metastases in Primary Melanoma Using FDG PET^a

Enlarged nodes? ^b	Author (reference)	Yr of publication	Number of patients	Histologically malignant/benign lymph node basins	Sensitivity of PET (%)	Specificity of PET (%)
Mixed group	Wagner et al. (29)	1997	11	7/7	100	100
Mixed group	Macfarlane et al. (31)	1998	23	13/11	85	92
No	Rinne et al. (30)	1998	52	15/37	100	94
No	Wagner et al. (34)	1999	74 ^c	18/71	11–17 ^d	94–100 ^d
No	Macfarlane et al. (31)	1998	9	1/8	0	88
No	Belhocine et al. (33)	2002	21	6/15	14	93
No	Havengna (32)	2003	53	13/40	15	88
Not defined	Acland et al. (75)	2001	50	14/36	0	NA ^e
Not defined	Schafer et al. (76)	2003	40	6/74	0	NA ^e
Not defined	Longo et al. (77)	2003	25	9/16	22	NA ^e
Not defined	Hafner et al. (78)	2004	100	26/74	8	100

^aAll patients were recently diagnosed with cutaneous melanoma and had no histopathologic evidence of regional lymph node metastases.

^bEnlarged lymph nodes by either clinical exam, ultrasonography or CT.

^c4 of 74 patients had recurrence at or adjacent to the surgical site and 70 had primary thick melanoma. No patient had enlarged nodes.

^dVariable range depending on ROC threshold.

^eCannot be determined from presented data.

Abbreviation: NA, not available.

Initial staging of patients with positive sentinel lymph nodes

There has been little work done looking specifically at PET or PET/CT in individuals with positive sentinel lymph node biopsies who have no other clinical evidence of metastatic disease. Presumably, these patients are at higher risk of additional local metastases or occult distant metastatic disease compared with the majority of individuals with primary melanoma who have no sentinel node metastasis. One study has carefully looked at this patient population. In 2006, Horn et al. (37) performed FDG PET on 33 patients with positive sentinel lymph node biopsies and no other evidence of metastatic disease (Fig. 9). Nine of 33 patients had a positive PET scan; four had occult stage IV metastases, one patient had an occult primary lung cancer, two were false positives, and two patients refused further staging. There was one false-negative study. This work suggests that there may be a slightly greater than 10% (4 of 33) chance of detecting occult stage IV metastases with PET or PET/CT and also gives weak support to the possibility that individuals with cancer may be at slightly increased risk for additional primary tumors that may be incidentally detected on PET. Given the noninvasive nature of PET and PET/CT, further imaging with this modality after the discovery of sentinel node metastasis may be considered by many doctors and patients to be worthwhile. Identification of occult distant metastases might affect the decision to perform or not perform a complete regional lymph node dissection.

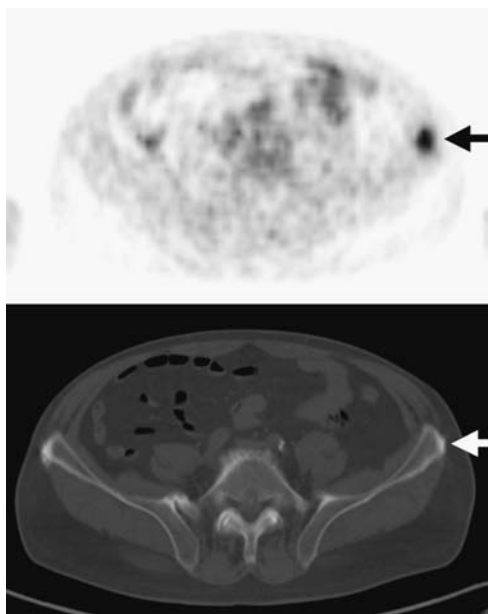


Figure 9 Occult metastatic disease. PET/CT demonstrates an intramedullary bone metastasis of melanoma that is not visible on CT alone.

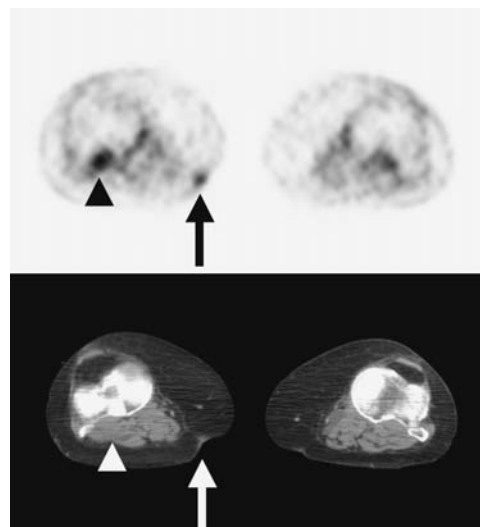


Figure 10 False positive. Patient with a past history of locally metastatic right calf melanoma. PET/CT demonstrates increased FDG uptake corresponding to scar tissue in the popliteal region (arrows) and physiological or inflammatory muscle activity (arrowheads).

Staging of patients with satellite or in-transit metastases or suspected primary tumor recurrence

There is limited data in the literature regarding the utility of PET or PET/CT in evaluating patients with suspected recurrence at the primary resection site (Fig. 10) or satellite metastases or in-transit metastases (Fig. 11). In a larger study with mixed patient populations, Acland et al. performed PET on nine patients with satellite metastases and found one true-positive lung metastasis and two false positives (38). Stas et al. looked at a mixed patient population with recurrent melanoma and found

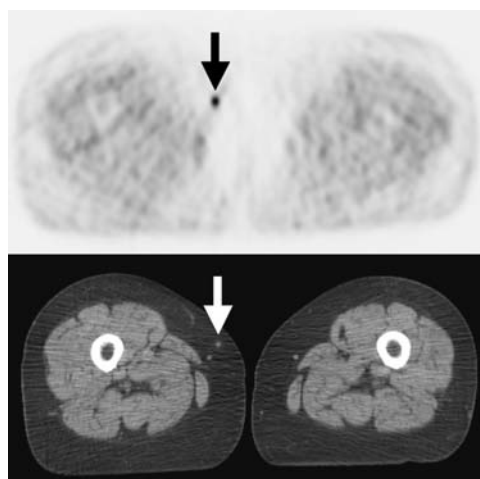


Figure 11 High sensitivity of PET/CT in metastatic melanoma. (Arrows) A 4 mm in-transit right thigh metastasis with intense metabolic activity.

that PET correctly downstaged an enlarged local lymph node in one of seven patients with locally recurrent melanoma. Evaluation of 18 patients with satellite or in-transit metastases by FDG PET led to a change in surgical management in three (Fig. 12) (39). Wagner evaluated four patients with in-transit metastases by FDG PET and found a sensitivity of 50% and a specificity of 100% for the detection of regional lymph node metastases (34).

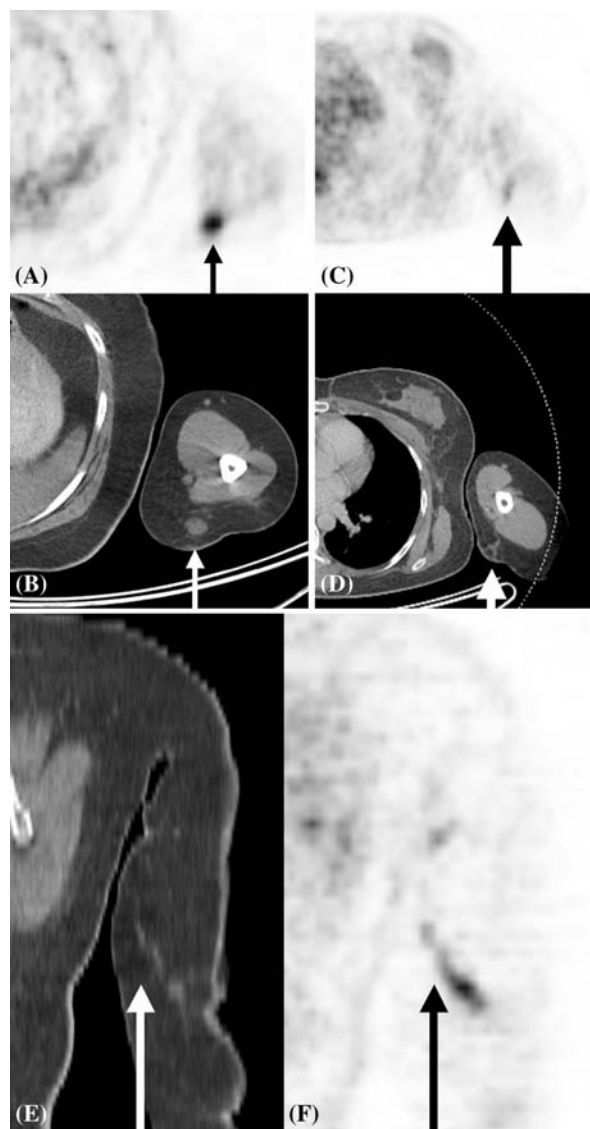


Figure 12 A 30-year-old female with two localized palpable foci of melanoma in the posterior left arm seen also on CT, MRI and transaxial PET/CT (arrows) (A–D). Coronal PET/CT reconstructions demonstrated more extensive disease involving the lymphatic channels of the left arm (arrows) (E–F). The patient was no longer considered a surgical candidate due to better definition of the extent of disease. Follow-up imaging confirmed the presence of diffuse tumor growing within subcutaneous lymphatics.

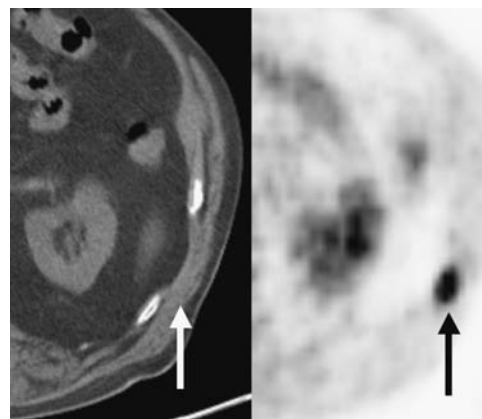


Figure 13 Detection of occult distant metastases. A patient with locally recurrent melanoma was found to have an occult distant intramuscular metastasis (arrows) that was not visible on CT and only detectable by PET/CT.

The above work does not allow an accurate determination of the utility of PET in these patient populations, and there is no data regarding the added benefit of PET/CT in these patients. In theory, the addition of CT to PET has the potential to aid the clinician in identification of small cutaneous or subcutaneous satellite or in-transit metastases that might have no measurable or only faintly visible increased metabolic activity on PET. Initial experience at our institution has demonstrated anecdotal cases where PET/CT allows identification of tiny cutaneous, subcutaneous, and intramuscular metastases that would not have been easily seen on PET or CT alone (Fig. 13). The combination of faint focal uptake on PET and a small soft tissue density on CT increases suspicion regarding the possibility of metastatic disease compared with one finding on PET or CT alone. Small lesions seen on PET/CT in individuals with clinically apparent local recurrence should be reported so that the surgeon can perform a more detailed physical exam and consider modification of surgical fields. 3D rendering of superficial lesions may also be helpful to direct physical exam and surgery. Further work is needed to determine the utility of PET/CT in these specific patient populations. For now it may be considered potentially useful to guide surgical resection of local metastases (Fig. 14) and will probably help detect occult distant disease in a few of these individuals.

Staging of patients with suspected locoregional lymph node metastases

Once there is clinical or conventional imaging (CT, ultrasound) evidence of local lymph node metastases, the probability of finding additional local lymph node metastases and/or distant metastases with PET or PET/CT increases. As seen throughout medical imaging literature, with a greater prevalence of disease, the accuracy of FDG

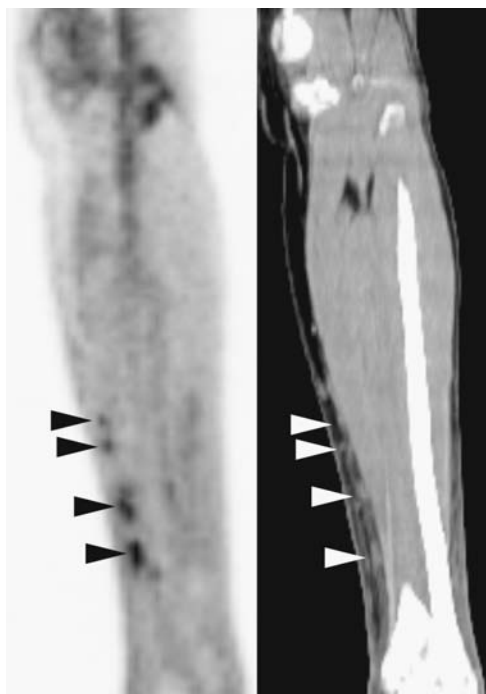


Figure 14 Defining extent of local recurrence. An 81-year-old female with locally recurrent metastatic melanoma of the left calf. Thick-slice maximum intensity projection PET and CT images clearly define the extent of subcutaneous disease. Careful review of CT images is useful to differentiate vascular inflammation from tumor foci.

PET or PET/CT would be expected to be higher. This expectation has been confirmed by several authors. Blessing et al. reported a 74% sensitivity and a 93% specificity for FDG PET detection of local lymph node metastases in patients with clinically enlarged nodes (40). Crippa reports an accuracy of 91% for detection of metastases in patients with enlarged lymph nodes on physical exam or conventional imaging. However, sensitivity was reported to be dramatically reduced (23%) for lymph nodes measuring less than 5 mm (41).

The clinical utility of detecting local metastases on PET or PET/CT in the setting of known enlarged lymph nodes might be called into question when most individuals would be subjected to biopsy of these nodes anyway. However, if one could use PET to exclude metastasis within enlarged nodes then patients could be spared unnecessary invasive procedures. To this end, Crippa's study demonstrated that 37 of 56 enlarged lymph node basins harbored metastatic disease and the negative predictive value was 89%. It is uncertain if a patient and referring physician would be satisfied with a negative PET scan in the setting of enlarged nodes given an 11% chance of false-negative findings. Questions remain regarding the potential use of FDG PET to bypass sentinel node biopsy

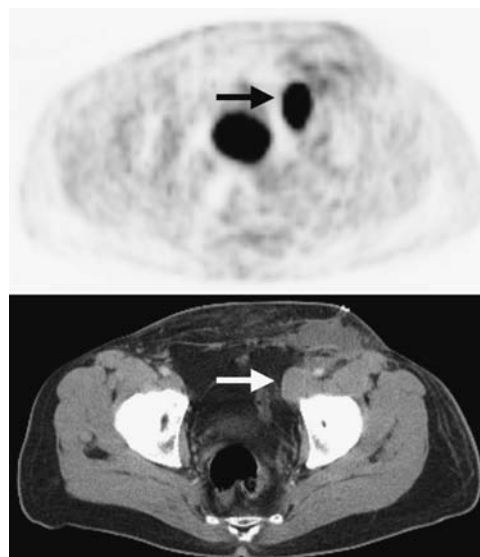


Figure 15 False-positive lymph node on PET/CT. A 55-year-old male with a history of left lower extremity melanoma and a positive left inguinal sentinel lymph node biopsy. Postoperative PET/CT was suggestive of a large metastatic left external iliac lymph node. Repeat surgical excision revealed a reactive lymph node.

and proceed directly to axillary dissection in patients with FDG-avid lymphadenopathy.

Although, perhaps not critical for evaluation of enlarged nodes, PET/CT might be expected to find occult distant metastases in the patient population that is at inherently higher risk for occult stage IV disease. One study by Tyler et al. addressed this issue by performing FDG PET on 95 patients with palpable local lymph nodes and/or in-transit metastases. A high false-positive rate for detection of all metastatic disease was found yielding a specificity of 43.5% (Fig. 15). Sensitivity for all types of metastases was higher at 87%. Importantly, 20% of all identified lesions represented previously unidentified occult metastases, and clinical management was altered in 16 of 106 (15%) patients (42). This one paper suggests that FDG PET or PET/CT has a definite role in the evaluation of patients with suspected nodal metastases, but clinicians and patients must be aware that there is a relatively high chance of false-positive findings in comparison with the detection of occult metastases. PET/CT may help improve with specificity compared with PET alone by identifying FDG uptake within benign structures, and further work needs to be done to explore this possibility. Nevertheless, a thorough understanding of benefit versus risk in these patients should be reviewed prior to ordering the study.

Staging of patients with known locoregional metastases

There are no studies looking specifically at the performance of PET or PET/CT in patients with known locoregional metastases only (Fig. 13). Fortunately, some studies

containing mixed populations of patients allow analysis of more focused subgroups. In a larger study containing melanoma patients with varying stages of disease, Wagner et al. performed FDG PET in seven patients with confirmed regional lymph node metastases and found four occult stage IV metastases including a left adrenal lesion, mediastinal metastasis, in-transit metastasis, and subcutaneous nodule (29). Similarly, Acland et al. found in a mixed population of patients with in-transit and regional lymph node metastases that 28% of patients undergoing FDG PET were found to have occult distant disease that might have altered patient management (38). When considering the above, albeit of somewhat limited validity, in addition to the possibility of additional lesion detection with PET/CT, some studies suggest that patients with known locoregional metastases will benefit from PET/CT.

Staging of patients with suspected or known distant metastases

With the emerging literature that favors the utility of PET or PET/CT in patients with sentinel lymph node or locoregional metastases, it would not be surprising to find that this modality is useful in individuals with known or suspected distant metastases. Potential uses would include confirmation of suspected metastases, localization of additional occult foci that might alter management, and acquisition of a baseline staging exam to help monitor response to systemic therapies.

There is a large body of literature addressing this group of patients which allows for solid recommendations

regarding the utility of PET and PET/CT. Gritters et al. performed FDG PET on 12 patients at varying stages of melanoma and reported a sensitivity of 100% for detection of intra-abdominal and visceral lymph node metastases, five of which were not initially seen on CT. Four occult skin and muscle metastases were found on PET and initially missed on CT. PET performed poorly for detection of subcentimeter pulmonary metastases (3), but PET/CT would have likely increased sensitivity at least, and perhaps specificity.

As part of a larger study, Rinne et al. performed PET on 48 individuals with CT or clinical evidence of local or distant metastases and found a sensitivity of 92% and specificity of 94% for PET compared with 58% and 45% for conventional imaging (30). Others have confirmed the advantages of PET compared with conventional imaging (43–45), with an important exception being detection of small lung and brain metastases in which CT and MRI are probably superior, respectively.

Overall, there is a clear rationale for the routine use of PET/CT in patients with suspected or known metastatic melanoma. In addition to confirmation of expected disease and detection of occult metastases, several authors have demonstrated that PET can change management in this patient population (44,45), primarily by the identification of occult lesions that are amenable to resection and also by cancellation of surgery that would not be beneficial because of the presence of additional unresectable lesions. Table 3 lists several key papers justifying the

Table 3 Detection of Melanoma Metastases Using FDG PET

Author (references)	Year of publication	Location of metastases	Sensitivity of PET (%)	Specificity of PET (%)
Gritters et al. (3)	1993	Abdominal	100	ND
		Lymph nodes	100	100
		Pulmonary	15	ND
		Skin and muscle	80	ND
Steinert et al. (79)	1995	All foci	92	100
Rinne et al. (30)	1998	Neck and abdominal lymph nodes	100	100
		Mediastinum	71	100
		Liver	100	100
		Abdomen	100	94
		Peripheral lymph nodes	97	100
		Bones	100	100
		Skin	100	100
Holder et al. (43)	1998	All foci	94	83
Eigtved et al. (45)	2000	All foci	97	56
		Abdomen	100	100
		Pulmonary/intrathoracic	100	NA
Swetter et al. (80)	2002	All foci	84	97
Gulec et al. (44)	2003	>1 cm lesions	100	75
		<1 cm lesions	13	33

Abbreviations: NA, not available; ND, cannot be determined from presented data.

use of PET and PET/CT for evaluation of metastatic disease.

Routine follow-up surveillance of asymptomatic patients

There are no studies that systematically evaluate when to use PET/CT in the follow-up of patients with a history of melanoma but who have no evidence of locally recurrent or metastatic disease. Appropriate guidelines would suggest PET/CT surveillance based on the risk of development of metastatic disease with a balanced consideration of financial cost, benefit from early detection and potential consequences of false positives. Given that no data is available, the only way to estimate when PET/CT might be helpful is to look at the data for initial staging. By roughly applying the above data, one could surmise that routine follow-up PET/CT will not be useful in most individuals who had negative sentinel lymph node biopsies. Patients with known local or distant metastases who have been resected might benefit from early detection of new metastases, and, therefore, a periodic follow-up PET/CT might be useful. It is difficult to make specific follow-up recommendations for the subgroup of individuals who had a positive sentinel node biopsy with a negative completion lymphadenectomy and no evidence of recurrent disease. The natural history of patients with positive sentinel nodes would suggest that follow-up PET/CT might benefit a few select individuals who eventually develop clinically occult but PET detectable, resectable, isolated distant metastases. Ultimately, no formal recommendation for this subgroup can be made until further work is done.

Prognosis

A general concept in cancer imaging is that patients with more extensive metastatic disease often have a worse prognosis. A more recent trend in PET and PET/CT imaging has been to use the prognostic power of the FDG concentration standardized uptake value (SUV) within primary or metastatic lesions. In 2006, Bastiaannet et al. determined that patients with higher SUV values (SUV mean >5.2) within local lymph node metastases had a shorter duration of disease-free survival compared with those with lower values. There was no measurable effect on overall survival and the authors proposed that future work should be done to determine if SUV levels in melanoma may be useful in determining if select patients would benefit from adjuvant radiation treatment or chemotherapy (46).

Treatment response

PET/CT imaging is increasingly used to assess response to therapy (Fig. 16) in an era where multiple chemotherapeutic and biologic agents are available to treat patients with metastatic cancer. This modality has the potential to

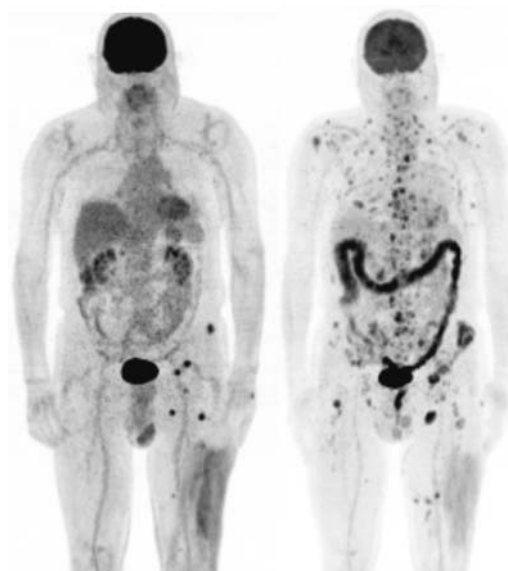


Figure 16 Assessment of treatment response. The whole-body capabilities of PET/CT accurately define the overall response to therapy. In this case there is extensive progression of disease.

detect metabolic alterations in tumors before they change in size (Fig. 17). Early responses to therapy can be predicted within one week of initiation of therapy in some tumors (47) by comparing the pretreatment uptake with midtreatment or posttreatment uptake.

There is scant literature specifically addressing the ability of PET or PET/CT to detect treatment response in melanoma. In 1999, van Ginkel and coworkers demonstrated that ^{11}C -tyrosine PET could predict response to isolated limb perfusion therapy (48). Similar findings were noted using FDG PET in the same clinical situation (49). Hannah et al. have reported the use of FDG PET in assessing response to radiation therapy in neurotropic desmoplastic melanoma (50). The use of PET and PET/CT in treatment response is potentially very useful but remains an experimental technique used primarily in clinical trials at major medical centers. It will likely be useful in assessing individual patient response to multidrug therapies.

Other tracers

Despite the advances associated with melanoma staging with PET/CT, the limitations of size, resolution, and specificity have prompted investigators to look at new tracers with potentially higher affinity for melanoma and/or greater rates of clearance from normal tissues. Such investigations thus far have met with limited success. The first study of an alternative PET tracer for melanoma was by Lindholm (51) and colleagues who demonstrated ^{11}C -methionine uptake in large melanoma lesions

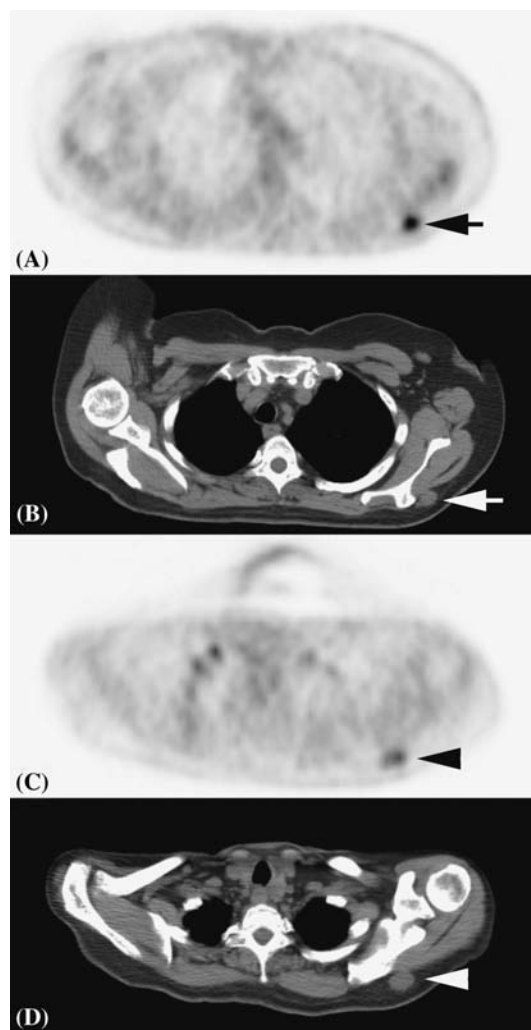


Figure 17 Partial metabolic response to therapy. A 66-year-old female with metastatic melanoma underwent PET/CT (A,B) demonstrating a left posterior chest wall subcutaneous metastasis with an SUVmax of 6.5 (arrows). The patient underwent chemotherapy and was restaged with PET/CT (C,D) four months after the initial study. Follow-up images demonstrate that the lesion has increased in size but decreased in metabolic activity (SUVmax = 2.7). The combination of PET and CT provides complimentary information regarding the tumor.

(>1.5 cm). Others have demonstrated uptake of ^{18}F -DOPA (52–54) and fluorinated thymidine (55) in melanoma metastases. Of particular interest is a radio-labeled alpha-melanocyte stimulating hormone analog that has the potential to specifically bind to melanoma cell membranes (56). It remains to be seen which of these tracers will become useful clinically.

New technical developments

In addition to the development of more sensitive and specific tracers, forthcoming technical developments

may improve the ability of PET/CT to accurately detect melanoma. In 2004, Solomon and coworkers reported the development of a CT-based computer-assisted-diagnosis algorithm that could detect and highlight small subcutaneous soft tissue densities on transaxial CT slices (57). Integration of this tool in to PET/CT interpretation software might help improve the detection of small in-transit or satellite metastases. Thinner CT slices reconstructed on new multislice PET/CT scanners (now offered up to 64 detector channels by select manufacturers) may also potentially improve lesion detectability.

Improvements in PET spatial resolution might also help detect smaller melanoma metastases that may not be visible with routine clinical scanners. Time-of-flight PET technology (58) is a promising new technique that better localizes the source of radioactive decay by detecting small, time differences between the arrival of annihilation photons on each side of the PET detector ring. Additionally, manufacturers are developing more efficient crystals and new reconstruction algorithms that may also improve image quality and lesion detectability. Additional techniques including 3D rendering of melanoma lesions seen at PET/CT and intraoperative FDG detectors (59–62) will likely contribute to improving the surgical care of patients with melanoma.

OTHER CUTANEOUS MALIGNANCIES

MCC

MCC is a rare neuroendocrine tumor of the dermis that occurred at a rate of 0.44 cases per 100,000 Americans in 2001 (63). This tumor frequently recurs both locally and at distant sites. At five years, only 60% of patients are free from distant metastases and the cause-specific survival is only 52% (64). Surgery remains the primary treatment modality and can be supplemented by radiation therapy and/or chemotherapy to reduce the rate of local recurrence (65). Accurate staging is essential for selection of appropriate therapy, but has not yet proven to impact overall survival.

The CT appearance of MCC was reviewed by Nguyen and colleagues in 2002 (66). High-attenuation adenopathy and soft tissue nodules are described as a common presentation on CT, and lymph node metastases are common in the neck, axilla, mediastinum, retroperitoneum, and groin. Soft tissue lesions are often noted in the chest or abdominal wall, and so is musculoskeletal invasion. Nguyen also demonstrated in their report that rim-enhancing metastases in the liver are common, and involvement of the stomach and bladder is also seen in advanced cases. Their group recommends MRI as the study of choice for evaluation of neurologic involvement.

The rarity of this tumor has limited any systematic evaluation of FDG PET or PET/CT in the staging and

management of MCC. There are, however, several case reports and a few case series demonstrating that PET can detect recurrent disease by means of the whole-body imaging capabilities and increased sensitivity for detection of small lymph node metastases compared with CT (67–69). One study also suggests that FDG PET may be useful for assessing response to therapy (70). FDG uptake is typically intense, with maximum SUV values for metastatic lesions ranging between 5 and 14 in one series (71). In summary, FDG PET/CT appears to be useful for initial staging, routine follow-up, and assessment of therapy response.

CSCC

CSCC (Fig. 18) is second only to BCC as a common cutaneous malignancy. Surgical resection is usually curative for most patients, and rare lesions behave in a locally invasive manner. There is only one paper referenced by the US National Library of Medicine discussing the utility of PET or PET/CT in CSCC. In 2005, Cho et al. (72) performed PET/CT on 12 patients with CSCC, which was clinically considered to be locally advanced in nine. The primary lesion was seen in all patients. Lymph node metastases were detected in 25% of patients and lung metastasis was found in one patient. Their study design did not allow calculation of sensitivity and specificity, but the findings suggest that there may be a role for PET/CT in staging patients with locally advanced CSCC.

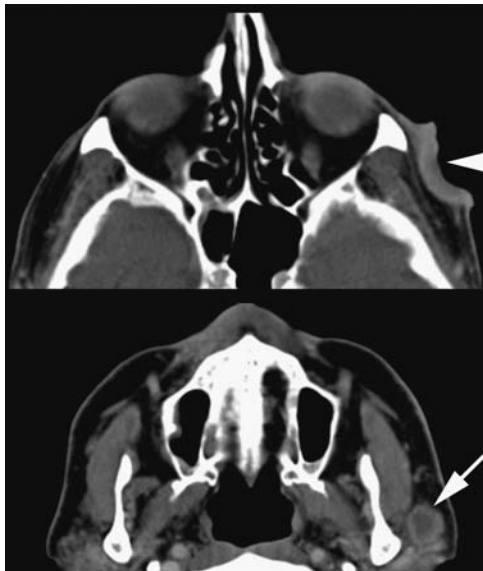


Figure 18 A 85-year-old male with a cutaneous squamous cell carcinoma of the left temple. IV contrast-enhanced CT demonstrates a moderately enhancing ulcerated primary tumor (*arrow-head*) and a periparotid lymph node metastasis with moderate peripheral enhancement and central necrosis (*arrow*).

BCC

There is only one paper looking at PET in the evaluation of cutaneous BCC (73). Fosko et al. examined six patients with BCC, four of whom had a nodular subtype and two with an infiltrative subtype. PET demonstrated the primary lesion in three of the four nodular subtypes and did not identify the infiltrative subtypes. One infiltrative tumor had perineural invasion that was not seen on PET. It is apparent that PET/CT in its current form does not have a defined role in the management of BCC.

SUMMARY

When used in the appropriate clinical situations, PET or PET/CT is a valuable tool for evaluation of patients with melanoma. There is no current evidence supporting the use of PET/CT for initial diagnosis of melanoma or for staging of primary melanoma when there are no clinical findings of concern for metastatic disease. There is emerging evidence supporting the use of PET/CT in staging patients with positive sentinel lymph node biopsies, and there is clear data supporting its use in patients with suspected or known local or distant metastases. In this situation, PET/CT is useful to direct surgery, detect occult distant metastases that might alter therapy, and assess response to therapy. There is no clearly defined role for routine follow-up screening of patients with resected thin melanomas and negative sentinel lymph nodes, but select patients at high risk for recurrence may potentially benefit from this technique. In general, any patient with findings of concern for metastatic disease, at any time during their care, will derive some benefit from PET or PET/CT. New tracers are being developed that aim to improve the sensitivity and specificity of PET/CT imaging for melanoma, and technical advancements including improvements in scanner resolution, computer-assisted detection algorithms, 3D visualization, and intraoperative PET probes hold promise for improving the care of patients with melanoma. Finally, PET/CT appears highly useful during the follow-up of patients with MCC, is of limited value in all but the most advanced patients with CSCC, and, at this point, is not indicated for individuals with BCC.

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PET/CT in Evaluating Lymphoma

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PET/CT IN EVALUATING LYMPHOMA

FDG PET and now FDG positron emission tomography/computed tomography (PET/CT) have essential roles in the initial staging, monitoring of therapy outcome, and follow-up of patients with lymphoma. Only primary central nervous system (CNS) lymphoma is assessed preferentially by magnetic resonance imaging (MRI) or CT. The interpretation of PET in concert with CT involves an understanding of the strengths, weaknesses, and normal criteria for both imaging modalities. To some degree, this has not been well defined for FDG PET.

Conflicting reports concerning the utility of qualitative, as opposed to semi-qualitative, i.e., standardized uptake value (SUV), data exist. While initially FDG uptake in normal-appearing lymph nodes may have been addressed with skepticism, the literature now supports the value of metabolic information. Conversely, the addition of anatomic information to the metabolic images significantly enhances the specificity of PET information and sensitivity for detecting metabolically active lymph nodes, especially when activity is moderate to mild. A review of the potential application of this powerful combination modality for lymphoma only underscores the need to use PET/CT in the management of lymphoma patients.

LYMPHOMA CLASSIFICATION

Malignancies of the lymphoid system include both leukemias and lymphomas. Leukemias generally involve the bone marrow and blood, while lymphomas are primarily involved with lymph nodes; but clearly there is a great deal of overlap. Systems for staging and categorizing lymphomas have evolved as our understanding of the histologic and cell marker characteristics as well as infectious etiologies has increased. For example, *Helicobacter pylori* infection has been identified as an etiology for gastric mucosa-associated lymphoid tissue (MALT) lymphoma. With improvements based on newer understandings of non-Hodgkin's lymphoma (NHL), the World Health Organization (WHO) classification, established in 2001 and based on the Revised European American classification of Lymphoid neoplasms (REAL), has been more widely adopted (Table 1) (1). The system divides lymphomas into B-cell, T-cell, and NK-cell neoplasms and Hodgkin's lymphoma. The B, T, and NK-cell neoplasms are separated into precursor and mature lymphomas, with, if possible, a cell of origin or stage of lymphoid differentiation assigned for each category. Despite the large number of entities, approximately 85% of all lymphomas are B-cell in origin and diffuse large B-cell lymphoma and

Table 1 WHO Classification of Lymphoid Malignancies

B-cell neoplasms
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia) (2%)
Mature (peripheral) B-cell neoplasms
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (6%)
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (with or without villous lymphocytes)
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B-cell lymphoma (with or without monocytoid B cells)
Nodal marginal zone B-cell lymphoma (with or without monocytoid B cells)
Follicular lymphoma (22%)
Mantle cell lymphoma (6%)
Diffuse large B-cell lymphoma (31%)
Mediastinal large B-cell lymphoma (2%)
Primary effusion lymphoma
Burkitt lymphoma/Burkitt cell leukemia (2%)
T-cell and NK-cell neoplasms
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
Mature (peripheral) T/NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1+)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sézary syndrome
Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, T/null cell, primary systemic type
Hodgkin's lymphoma (disease)
Nodular lymphocyte predominance Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma

Source: From Refs. 8,197,198.

follicular lymphoma account for more than half of all NHL (1).

Hodgkin's disease (HD) has a bimodal age distribution, affecting young adults and the elderly. HD has been

classically divided into four types: nodular sclerosing, mixed cellularity, lymphocyte predominance, and lymphocyte depleted forms. The more recent WHO classification has combined nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich Hodgkin's lymphoma under the category "classical Hodgkin's lymphoma." Nodular sclerosing lymphoma is the most commonly occurring form of Hodgkin's lymphoma in Western Europe and North America. Prognosis has been correlated with the presence of systemic symptoms, bulk of tumor, histologic type, extranodal extension involving the spleen, bone marrow, or liver, immunophenotype and other immunologic, hematologic, and biochemistry data (2). The mixed cellularity type is more common outside these geographic areas and in poorer populations within North America, and usually presents with B symptoms. The lymphocyte-rich type has been associated with a more favorable prognosis. The lymphocyte-depleted type, which may overlap with NHL, has been demonstrated to have the worst prognosis of the four subtypes. Although histologic type does contribute to prognosis, it may not be as strong an indicator as initially considered (2).

Nodular lymphocyte-predominance Hodgkin's lymphoma has been placed into a separate category and lacks the Reed–Sternberg cell identified in the classical Hodgkin's lymphoma forms. Nodular lymphocyte-predominance Hodgkin's lymphoma has a more indolent course (3) (Table 1).

HD accounts for 40% of pediatric lymphomas, with mixed-cellularity and nodular sclerosing types predominant in preadolescent patients. Nodular sclerosing HD is common in the adolescent patient population. In the pediatric population, overall survival rates are approximately 90% (4). Treatment of HD usually includes both chemotherapy and radiation.

NHL is more common than HD. NHL has been linked to immune deficiency including posttransplantation, HIV, congenital immune deficiencies, autoimmune disease including Sjogren's syndrome, infection, such as Human Herpes virus 8, Epstein–Barr virus, HTLV-1, Hepatitis C, and *Helicobacter pylori*, and occupational and environmental exposures (5). NHL is composed of a broad spectrum of lymphomas with widely varying levels of behavior. Indolent lymphomas include follicular and marginal zone lymphomas. Typically, patients with these lymphomas have painless lymphadenopathy with slow progression. Extranodal involvement and symptoms are less common in the early stages of disease (3). More aggressive lymphomas include diffuse large B-cell lymphoma and Burkitt lymphoma. The majority of patients with high-grade lymphoma have lymphadenopathy at presentation, although, in distinction to the indolent lymphomas, many have extranodal involvement involving the gastrointestinal tract, bone marrow, sinus regions, thyroid,

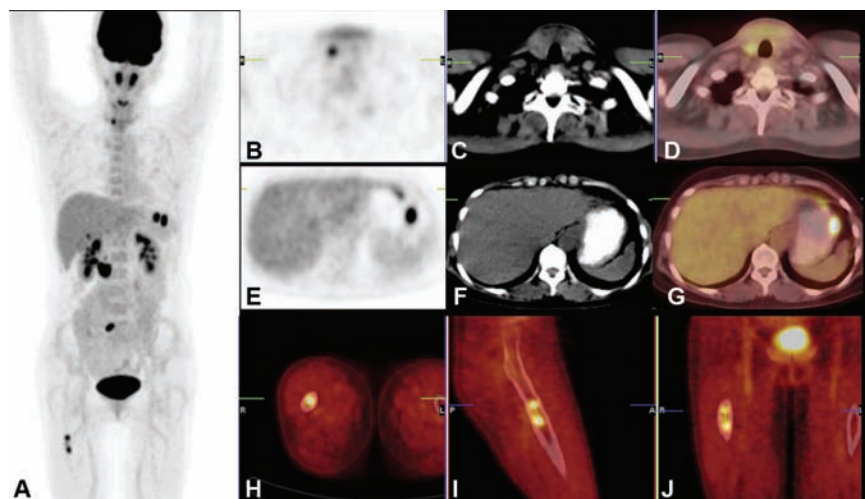


Figure 1 A 43-year-old woman who presented with a thyroid nodule found to be a Burkitt lymphoma. Anterior view of an MIP from an FDG PET/CT (A) performed for initial staging show intense uptake in the thyroid, two foci of uptake in the gastric wall, and uptake in the right femoral shaft. (Top row) Transaxial PET (B), corresponding CT slice (C), and PET fused to CT (D) shows the intense uptake in the thyroid lymphoma, which is slightly hypodense on CT. (Middle row) Transaxial PET (E), corresponding CT slice (F), and PET fused to CT (G) shows FDG activity fused to a relatively bland appearing gastric wall on CT scan. (Bottom row) Transaxial (H), sagittal (I), and coronal (J) fused images from the same study demonstrates the activity corresponding to the lymphoma involving the marrow of the femoral shaft.

or CNS as well. One-third of high-grade lymphoma presents with symptoms (3) (Fig. 1).

In children, NHL tends to be more aggressive and more commonly presents early on in the course of the disease with extranodal disease, especially in bone and the CNS. Burkitt lymphoma, lymphoblastic, anaplastic large cell lymphomas, and large B-cell lymphomas—all high grade—are the more common NHLs found in the pediatric age group, but overall survival in the children and adolescents for NHL is relatively better than for the adult population, approaching 75% (6). NHL is most often treated initially with a multidrug chemotherapy regimen. More recently, therapy for B-cell lymphomas can include a combination of immunotherapy, radioimmunotherapy, and/or chemotherapy.

DIAGNOSIS AND STAGING OF SYSTEMIC LYMPHOMA

For diagnosis of HD and NHL, excision of a suspicious node is typically performed for histologic analysis and immunophenotyping (7). Following diagnosis, accurate staging is critical, since a large percentage of both Hodgkin's and NHL are curable if appropriate therapy is administered (8). Particularly for children with a higher probability of cure, more recent efforts have focused on appropriately limiting the radiation therapy dose and field in addition to tailoring the number of chemotherapy

cycles. Some of the long-term side effects observed in survivors of childhood lymphomas may thus be avoided. Imaging plays an essential role in staging both for HD and NHL.

Staging of both HD and NHL are based on the Ann Arbor system, which was originally developed to stage HD (Table 2). This system has been somewhat modified for NHL since the incidence and prognostic implications of extranodal disease and bone marrow involvement for these lymphomas differ from that in HD (8). Bone marrow involvement occurs in approximately 25% of patients of NHL and 10% of HD patients at diagnosis. Liver involvement occurs in 15% of patients with NHL but in only about 3% of HD at initial diagnosis. The spleen is involved in about 23% of patients with HD and 22% of NHL patients at diagnosis (9,10).

Staging includes history and physical examination, laboratory evaluation, bone marrow biopsy, and imaging. CT scan is currently the standard for imaging, primarily CT of the chest, abdomen, and pelvis (11–13). FDG PET is increasingly regarded as adding accuracy to the staging of lymphomas (6,14–17). For HD, staging laparotomies are no longer performed. Gallium scanning has largely been supplanted by FDG PET for both NHL and HD (11,18–21) and FDG PET has been judged to be cost effective (19). Although mostly concordant, experience has shown that PET and CT may provide complementary information in children in particular (6,11,12). Not unexpectedly, these discrepancies occur in residually enlarged

Table 2 Ann Arbor System of Staging

Stage	Features
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E; any involvement of bone marrow, liver, pleura, CSF
For all stages	
A	No symptoms
B	Fever ($>38^{\circ}\text{C}$), drenching sweats, weight loss (10% body weight over 6 mo)
For stages I to III	
E	Involvement of a single, extranodal site contiguous or proximal to known nodal site; any involvement of bone marrow, liver, pleura, CSF is considered stage IV

Source: From Ref. 8.

nodes that are PET-negative after treatment, with small pulmonary nodules on CT that are below the resolution limits of PET, and with thymic and marrow hyperplasia at various stages after therapy.

Anatomic Distribution of Disease at Staging

HD presents with involvement of the thorax in 80% of the cases (22). Commonly, lymph nodes are involved most frequently in the anterior mediastinum with subsequent spread to bone marrow and extranodal sites, most commonly the spleen, lungs, liver, and bone marrow. With NHL, the thorax is involved at presentation 45% of the time (23). Primary lymph node involvement may also occur within the abdomen.

CT in the Staging of Lymphoma

Both HD and NHL manifest as enlarged nodes on CT. Within the thorax, lymph nodes are considered enlarged when greater than 1.0 cm in short axis. In the mediastinum, adenopathy, when present, is typically asymmetric when comparing right and left sides. Symmetry of mediastinal and hilar adenopathy should lead to a consideration of sarcoidosis, although the clinical scenarios, such as the presence or absence of symptoms and other imaging findings such as parenchymal disease, should be considered.

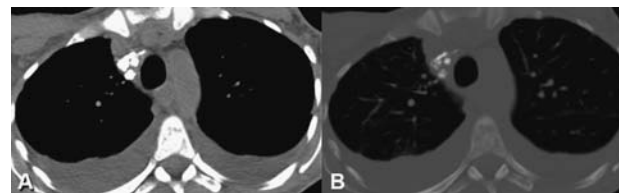


Figure 2 A 41-year-old woman who had a remote history of Hodgkin's disease with new onset of acute myelogenous leukemia and shortness of breath. CT scan of the chest with soft tissue windows (A) and bone windows (B) shows bilateral pleural effusions secondary to congestive heart failure and cardiomyopathy as well as the typical calcifications in treated right paratracheal lymph nodes.

Nodes are typically of soft tissue density; however, enhancing and low attenuation necrotic nodes also have been described. Lymph nodes do not typically contain calcification unless coexistent disease such as previous granulomatous disease is present. Only rarely has calcification in HD and NHL been described prior to therapy (24). After treatment with radiotherapy or chemotherapy, lymph node calcification, however, can occur (25–27) (Fig. 2). In this scenario, calcification may range from very punctuate to dense (25).

HD classically presents as a large anterior mediastinal mass (Fig. 3), although less common forms of HD may present differently. Enlarged nodes may be present in the middle and posterior compartments, but rarely in the absence of anterior mediastinal disease. Differentiating anterior mediastinal HD from other etiologies of anterior mediastinal masses may be difficult. Discrete enlarged or nonenlarged lymph nodes in the vicinity of an anterior mediastinal mass are suggestive of lymphoma rather than thymic or germ-cell neoplasms. Hilar lymphadenopathy without mediastinal involvement in HD is uncommon. Direct invasion of the lung parenchyma by mediastinal lesions can also occur (22). Chest wall involvement can occur, as described in 6.4% of cases in a study by Castellino et al. (22).

NHL often presents as lymphadenopathy in the mediastinum. In a study of CT for staging NHL, most common sites of mediastinal involvement were in the prevascular and paratracheal regions followed by the subcarinal, hilar, posterior mediastinal, and cardiophrenic angle regions (23). Differentiation between HD and NHL is difficult when presented with an anterior mediastinal mass, although anterior mediastinal and internal mammary lymphadenopathy is more common in patients with HD than NHL (28). However, lymphadenopathy in the thorax with primary posterior mediastinal involvement is more likely to be NHL than HD. NHL has a tendency for isolated and noncontiguous spread (28).

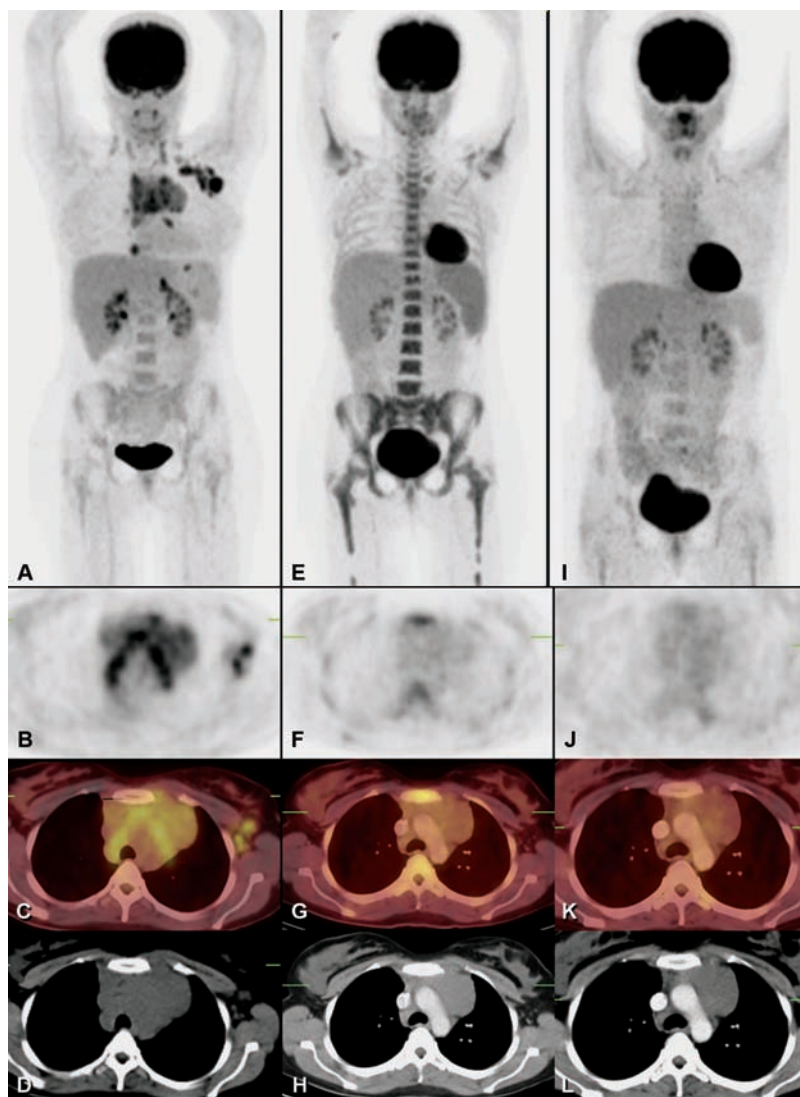


Figure 3 A 22-year-old woman with Hodgkin's disease. Anterior view of an MIP image (A) from the initial staging FDG PET/CT shows increased anterior mediastinal activity in addition to left axillary, cervical, and mediastinal adenopathy as well as focal splenic uptake. The transaxial PET (B), fused image (C) shows diffuse uptake corresponding to the anterior mediastinal mass on CT (D) as well as uptake in lymph nodes. After two cycles of chemotherapy, the lymph node and anterior mediastinal activity had resolved significantly, as seen on the anterior view of the MIP (E), transaxial PET (F), and fused images (G). However, significant mass remains on the contrast-enhanced CT (H). At the end of chemotherapy and prior to radiation therapy, the restaging PET/CT shows resolution of abnormal activity on the anterior MIP (I), the transaxial PET (J), and fused images (K). The CT (L) continues to show residual, anterior mediastinal soft tissue.

Lymphoma may achieve a large size before exhibiting significant mass effect on structures. Encasement of structures can occur (Fig. 4). Superior vena cava syndrome and biliary obstruction, however, occur particularly with advanced and bulky disease.

Extranodal sites can be involved by disseminated systemic lymphoma. In HD, pleural or subpleural nodules of varying sizes and of varying borders can be demonstrated on

CT in the lung parenchyma (Fig. 5). Necrosis and cavitation can occur. A less common pattern is a miliary or reticulonodular pattern that may be difficult to differentiate from sarcoidosis or lymphangitic carcinomatosis. Airway obstruction can occur related to lesions in the wall of the bronchi. Pleural effusion can be identified in 10% to 13% of cases on diagnosis. Focal destruction of osseous structures related to direct extension of tumor can occur (22). When

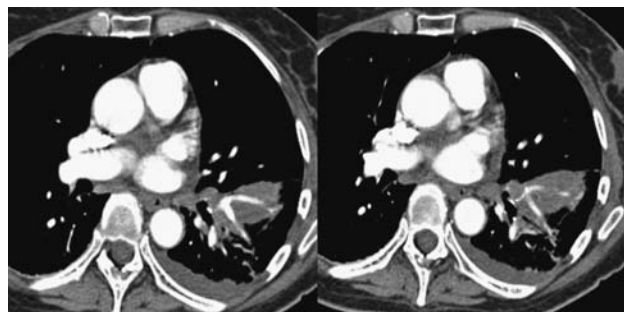


Figure 4 A 62-year-old female with lymphoma. On axial contrast-enhanced CT images the vessels remain patent despite passing through considerable soft tissue abnormality in the hilum and lung parenchyma.

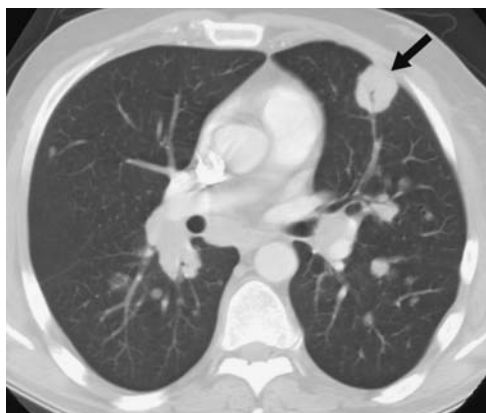


Figure 5 Axial CT scan in a 42-year-old male with Hodgkin's disease demonstrates nodular densities in the lung parenchyma. One of the nodular densities has air bronchograms (*arrow*). Adenopathy in the subcarinal bilateral hilar regions are also present in this individual with systemic lymphoma.

lymphoma involves the bone marrow, ivory vertebra may be present on CT and may be accompanied by lytic osseous lesions. Spleen involvement manifests as diffuse enlargement with possible focal areas of decreased attenuation.

In NHL, solitary and multiple nodules or masses in the lungs can occur and have varying sizes ranging from 5 mm to 8 cm. A lower-lobe predominance and poorly defined margins have been noted. Cavitation can occur, although rare. Involvement of large-sized airways has been noted, likely related to direct extension from nodal disease. A reticulonodular pattern has also been reported, mimicking lymphangitic carcinomatosis or sarcoidosis (29). Air-space consolidation and ground glass opacities can occur. Pleural involvement may manifest as an effusion. However, more common presentations are mass-like

or focal areas of thickening, nodules, masses, or less commonly, diffuse pleural thickening. Extranodal locations can serve as the primary location for lymphoma.

FDG PET Imaging

FDG PET is increasingly regarded as adding accuracy to the staging of lymphomas (14). PET imaging adds to the standard assignment of lymphadenopathy when lymph nodes are 1.0 to 1.5 cm or greater on CT (8). Some controversy or uncertainty still pertains to what constitutes abnormal uptake in lymph nodes on FDG PET. While some require more intense uptake than soft tissue background (15), with the use of inline PET/CT, there is improved recognition of low-level metabolic activity in normal-sized lymph nodes. However, the significance of low-level, mild uptake in normal-sized hilar lymph nodes is under some debate and often disregarded when identifying lymphomatous involvement (13). Even more controversial is the role of FDG PET in staging bone marrow involvement and the possibility of replacing or augmenting bone marrow biopsy with PET (14).

FDG PET in Comparison with CT

Most studies to date compare the accuracy of FDG PET with that of CT (6,14–17) rather than assessing the benefit of using the two modalities in concert. In most studies, concordance between CT and PET in staging is more frequent than not (11–13). However, the addition of PET to conventional imaging modalities, usually CT, does increase the sensitivity for detection of lesions (11,18–21) and has been judged to be cost effective (19). In children, although PET and CT again are mostly concordant, they may provide complementary information even more often than they do in adults (6,11,12).

In general, PET alone has been shown to be more sensitive than CT alone. While the vast majority of regions of involvement are detectable on both PET and CT, PET tends to be more sensitive, especially for involvement of organs such as the spleen, bone, or liver (11,17,18,21,30). For example, sensitivity of PET/CT for splenic involvement is higher than for contrast-enhanced CT alone (17,31). Lymphoma in the spleen may be diagnosed on CT by identifying splenomegaly or focal lesions (32), while PET demonstrates splenomegaly or focal or diffuse increased uptake (17,21,30) (Fig. 6). However, CT predictably is more sensitive for lung lesions (20) than PET, given the lower spatial resolution of PET (21). In a number of studies, FDG PET has led to upstaging (14,21,33) as well as downstaging (21,33) of the disease in comparison with conventional modalities, including bone marrow biopsy and CT (Table 3).

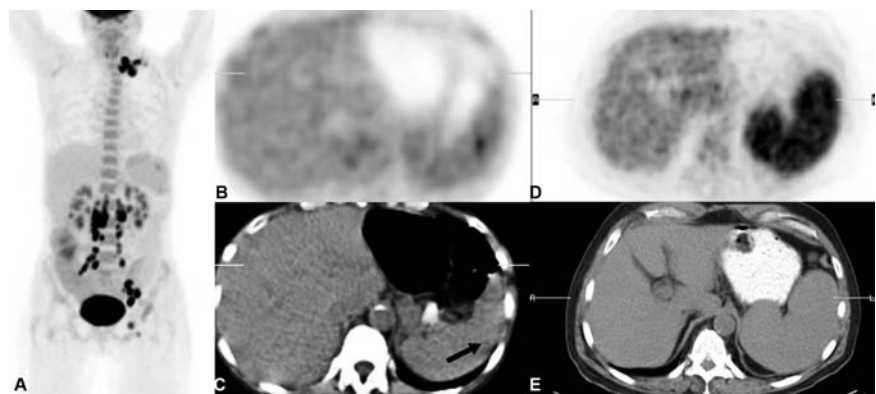


Figure 6 A 67-year-old woman with both T-cell lymphoma and Hodgkin’s disease. Anterior view of an MIP image (A) of the FDG PET performed for restaging after the patient presented with a neck mass shows extensive retroperitoneal lymphadenopathy, left inguinal, and left supraclavicular adenopathy. A focus of increased uptake and diffusely increased uptake in the spleen compared with the liver can be appreciated on this image. Transaxial PET section through the spleen (B) shows a focus of increased uptake that corresponds to a barely perceptible hypodensity in the spleen (arrow) on the corresponding CT image that is adjacent to artifact related to adjacent bone (C). In another patient, a 75-year-old man with angioimmunoblastic lymphoma underwent PET/CT because of suspected recurrence eight months after completing chemotherapy. The FDG PET slice (D) shows intense and diffuse splenic uptake. The CT slice (E) suggests an enlarged spleen. It measured 17 cm in vertical span on coronal images (not shown).

Table 3 Influence of PET on Initial Staging

Authors (Ref.)	Accuracy	Overall change in management	Percentage upstaged	Percentage downstaged
Schoder et al. (33) (HD and NHL)		62%	21%	23%
Naumann et al. (199) (HD only)		18%	13%	8%
Jerusalem et al. (200) (HD only)	90%	3%	9%	9%
Menzel et al. (201) (HD only)		21%	14%	7%
Wirth et al. (18) (HD and NHL)	95%	18%	14%	
Weihrach et al. (20) (HD)	88%	9%	18%	
Partridge et al. (21) (HD)		25%	41%	7%
Stumpe et al. (137) (HD and NHL)	86%			
Tatsumi et al. (13) (HD and NHL)			7%	9%
Schaefer et al. (31)	93% (LN) 100% (EN)	16%		
Hutchins et al. (35)	92% (LN) 73% (EN)	7%	17%	5%
Depas et al. (11) (Pediatric)	95%	10.5%	5.25%	5.25%
Miller et al. (12) (Pediatric)	97%	32.3%	22.6%	9.6%

Abbreviations: LN, lymph nodes; EN, extranodal disease; HD, Hodgkin’s disease; NHL, non-Hodgkin’s lymphoma.

PET/CT Efficacy

Studies of in-line PET/CT underscore the utility of correlated images in lymphoma staging. FDG uptake can correspond to normal-sized lymph nodes and indicate pathologic involvement. Alternatively, mild FDG uptake, not clearly recognizable on PET alone, can become evident when seen to correspond to enlarged lymph nodes on CT. The benefit of dual modality information has been shown to improve the accuracy of staging in a number of studies (13,34), particularly for extranodal disease. PET/CT has been reported to have slightly greater sensitivity and

specificity for nodal disease than contrast-enhanced CT, while for detection of extranodal disease, PET/CT significantly outperforms contrast-enhanced CT in terms of sensitivity. Predictably, PET/CT identifies disease in unenlarged lymph nodes and thymus, as well as spleen, bone, liver, pancreas, and bowel (17,31). PET/CT has been shown to add specificity to PET for nodal staging in the abdomen and possibly for extranodal disease (35) (Fig. 7). Lastly, non-specific PET uptake, such as uptake in brown fat, is more clearly identified on PET/CT (13). Improved accuracy has also been reported for pediatric and adolescent patients (12), where PET/CT upstaged over

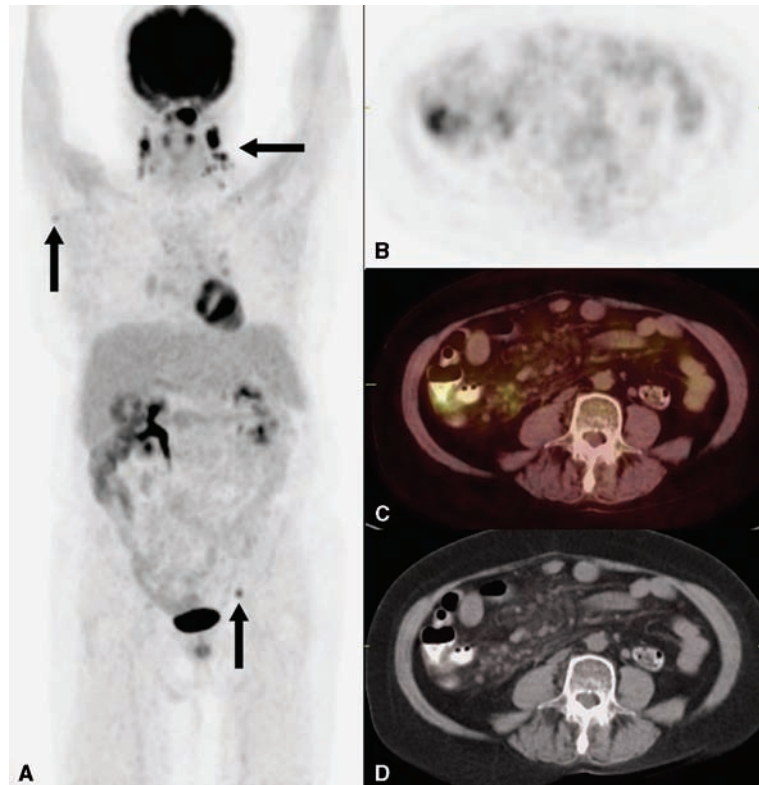


Figure 7 A 83-year-old man with large B-cell lymphoma who recurred in cervical and right axillary and left inguinal lymph nodes (arrows) as seen on the anterior view of the MIP (A). Transaxial images through the abdomen demonstrate rather bland uptake on the FDG PET image (B), which when fused (C) to the corresponding axial CT section (D) clearly corresponds to additional lymphadenopathy in the mesentery.

one-fifth and downstaged almost one-tenth of patients compared with CT alone. In this population, thymic uptake can be problematic in staging of lymphoma. In children particularly, the normal thymus may be active. Therefore, activity on PET alone due to lymphomatous involvement may be overlooked as normal (11). In this setting, the anatomical configuration of the corresponding anterior mediastinal soft tissue on CT is helpful in differentiating normal thymic uptake from lymphoma.

PET/CT in Assessing Extranodal Bone Marrow Involvement

Bone marrow involvement confers an advanced stage of disease. While the incidence of bone marrow involvement in low-grade lymphomas is quite high, less than half of the patients with high-grade NHL present with bone marrow involvement and less than 15% of the patients with HD have documented marrow involvement at presentation.

Bone marrow staging is typically performed by bone marrow biopsies, although the need for biopsy in already

advanced disease has been questioned (36). PET imaging may contribute to the staging of the bone marrow. The sensitivity of PET in assessing bone marrow involvement is best when evaluating HD and higher-grade NHL in patients with greater degrees of bone marrow involvement (12,17).

FDG PET alone has been shown to be more sensitive than CT in the depiction of bone marrow disease in both HD and NHL in adults (12,17) (Fig. 1) and in the pediatric age group (12). Additionally, FDG PET is increasingly the standard modality used in place of bone scintigraphy for assessing bone and bone marrow involvement. In a series of 64 patients with either HD or NHL, bone scan and PET were negative in 61% and agreed with bone marrow histology from all of the patients who underwent biopsy (37). When bone scan and PET were concordantly positive, bone marrow involvement was confirmed even when initial biopsy was negative (37). More importantly, PET in this study identified involvement in five patients in whom bone scintigraphy was negative and in two in whom marrow biopsies were negative; these patients had either HD or a high-grade NHL.

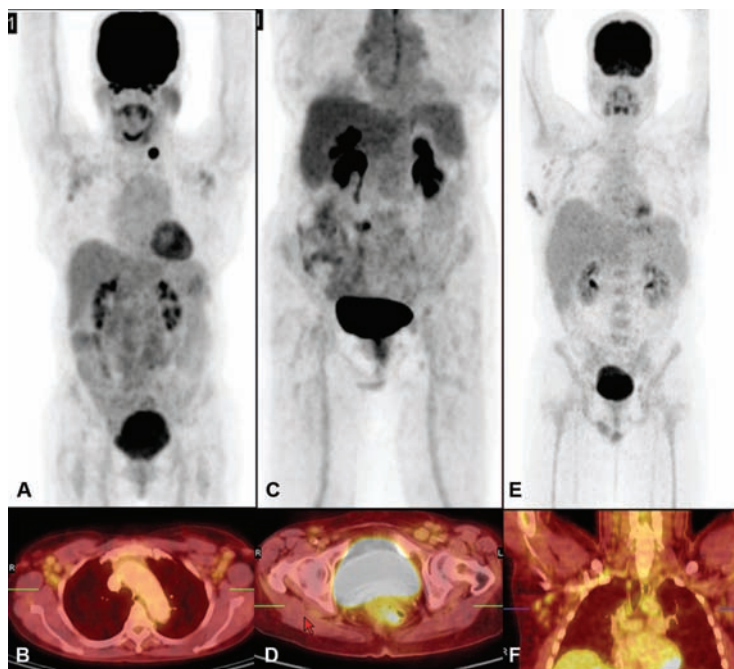


Figure 8 (A) Anterior view of an MIP from an FDG PET/CT performed on a 73-year-old woman with a small cell lymphocytic lymphoma with increasingly bulky adenopathy. (B) Transaxial fused PET and CT images show low-level activity in multiple enlarged bilateral axillary lymph nodes. (C) Anterior view of a MIP from an FDG PET/CT performed for staging on a 79-year-old woman with mantle cell lymphoma diagnosed by palatine tonsil biopsy shows subtle bilateral inguinal lymph node uptake. (D) Transaxial fused PET and CT shows mild uptake fusing to multiple enlarged inguinal lymph nodes. (E) Anterior view of an MIP from an FDG PET/CT performed on a 65-year-old man with a long history of chronic lymphocytic leukemia for monitoring of possible Richter's transformation shows low-level uptake in right axillary lymph nodes. (F) Coronal fused PET and CT shows the activity corresponds to the multiple enlarged nodes.

Although not always concordant, FDG PET and bone marrow biopsy may each serve to upstage patients by detecting bone marrow involvement. PET can detect disease in the bone marrow beyond the area sampled during an iliac crest bone biopsy (36,38,39). PET, however, may also be negative or equivocal in patients with positive iliac crest biopsies related to low density of marrow infiltration and low-grade tumors (38–41).

A meta-analysis of 587 patients comparing PET with bone marrow biopsy yielded a sensitivity of PET of 51% with a specificity of 92%. In many of the studies included in the meta-analysis, there were patients in whom bone marrow biopsy was negative, but PET showed focal marrow involvement (42). In one series that included patients with HD and NHL (38), bone marrow biopsy was positive while PET was negative in 5% of the patients. In those patients with positive marrow biopsies but negative PET scans, the density of lymphoma was low with 10% or less of the bone marrow involved. Also, the grade of lymphoma was either low or intermediate. However, in this study PET identified bone marrow involvement in spite of negative biopsies in 10% of the 78. In another series (36) that also included HD and NHL, 16% of the patients in the study had positive bone marrow on PET scans with

negative biopsies. Of those eight patients, those with focal PET findings were true positives. Diffuse increased marrow uptake was unexplained except for one case that was related to marrow hyperplasia. In two of the three patients with negative PET but positive marrow, other sites involved by low-grade lymphoma were also not visualized by PET, suggesting a low sensitivity of PET for those tumors. The third patient had mantle cell, a lymphoma with variable uptake on FDG PET (36) (Fig. 8). In 106 cases of lymphoma with 28 having bone marrow involvement, FDG PET had a sensitivity of 86% for marrow involvement. Four cases of follicular lymphoma, positive on biopsy were negative on PET (39). Thus, FDG PET has a high positive predictive value but is not a reliable negative predictor. In terms of in-line PET/CT, the efficacy in terms of bone marrow involvement has not yet been systematically studied.

EXTRANODAL PRIMARY LYMPHOMA

Extranodal primary lymphomas represent about half of all NHL. Typically, the disease is confined to the organ or organ and regional lymph nodes. The gastrointestinal tract

is the most common site of extranodal lymphoma (43–45), but lymphoma can arise in pancreas (46), liver (47), adrenal (48–50), kidney (51), testes, ovary (52), uterus (53), breast (54), lung (55), myocardium (56), bone (see primary skeletal tumors), conjunctiva (57), dura (58), and CNS, of which intraocular lymphoma is considered a variant (59). FDG PET plays a role in upstaging and monitoring those patients with large enough volume disease to be seen.

Gastrointestinal Tract

Gastric lymphomas are the most common extranodal primary lymphomas and may occur simultaneously in the presence of gastrointestinal stromal tumors (GIST) (60). A majority are either low-grade marginal zone MALT tumors or diffuse large B-cell lymphomas, but T-cell lymphomas and mantle cell types also occur (56,61,62). Gastric MALT lymphomas have been associated with *Helicobacter pylori* (63) and respond to eradication of this organism (64). Overall five-year survival, regardless of histologic type, is greater than 90% (62); however advanced age, male gender, elevated lactate dehydrogenase, and ascites are poor prognostic factors (61).

On CT, low-grade MALT lymphoma appears as diffuse infiltration and wall thickening that is difficult to identify when the stomach is nondistended (65). Ulcerative, polypoid, and nodular lesions have also been described (66). Extension outside of the stomach by tumor is not common, although lymphadenopathy can be present (67–69). Higher-grade lymphomas demonstrate more mass-like areas and severe fold thickening than low-grade MALT lymphomas (69). Park et al. reported a mean fold thickening of 2.5 cm for high-grade gastric lymphoma in comparison with 0.8 cm for low-grade MALT lymphoma (69). FDG uptake in these lymphomas can be intense (Fig. 9) but must be differentiated from other malignancies and benign causes. Potentially, the diagnostic value of FDG may be improved by conducting a well-performed CT with adequate gastric distention at the same time.

Primary lymphoma of the gastrointestinal tract can occur in the small bowel, colorectal region, and esophagus. Primary small bowel lymphoma is relatively uncommon, with the majority of lymphomas being the non-Hodgkin's variety of B-cell origin. Low-grade MALT lymphomas have been reported to represent approximately 19% of primary small bowel lymphomas (45). Lymphoma of the small bowel most commonly affects the distal ileum, which contains a greater amount of lymphoid tissue. Lymphoma can complicate celiac disease, occurring typically in the proximal jejunum. Lesions are typically within the wall of the small bowel and affect long segments of bowel, mainly when involving the circumference of the lumen. Aneurysmal dilatation of the bowel occurs when muscularis propria is replaced by lymphomatous tissue affecting the autonomic nerve plexus. However, luminal diameter may be preserved or narrowed with subsequent obstruction, although uncommon. The mucosal surface of the bowel can appear smooth on small bowel series secondary to submucosal infiltration by tumor. Extension of the small bowel masses beyond the serosa into the mesentery can occur. Ulceration of lymphomatous masses can lead to fistula formation, with appearance similar to that of cavitary GIST and cavitating metastases. Multicentric small bowel lymphoma can occur leading to a multinodular pattern, which is associated more frequently with generalized lymphoma and immunodeficiency states (45,70).

Primary lymphomas of the colorectal region are much less common than those of small bowel origin. Primary colorectal lymphomas comprise about 10% to 20% of gastrointestinal lymphomas but less than 1% of large bowel tumor. Histology tends to be diffuse large B-cell lymphomas, although other types occur. An association of large bowel lymphoma with immunosuppression or ulcerative colitis has been described. Colorectal lymphomas can present as polypoid lesions that may ulcerate. Diffuse involvement can also occur, with concentric narrowing on CT, and a multinodular form may mimic familial polyposis syndrome with varying size of multiple nodules (70). Primary colorectal lymphomas present frequently with regional node involvement (44). The reported five-



Figure 9 A 44-year-old man with primary NHL of the stomach prior to therapy. Increased uptake on axial FDG PET (A) fuses (B) to the thickened wall of the gastric antrum on axial CT section (C). *Abbreviation:* NHL, non-Hodgkin's lymphoma.

year survival for patients is only 27% to 52% (44). Since most of the colorectal lymphomas are high grade, they are expected to be FDG avid, but little exists currently in the literature to document this.

Abdominal and Pelvic Solid Organs

Primary pancreatic and liver lymphomas are rare. Primary pancreatic lymphoma may occur as a focal lesion in any region of the pancreas or may be diffusely infiltrating (46). Accompanying pancreatitis has been reported (46,71). B-cell types are more prevalent (72). On CT, peripheral enhancement of the lesions has been described (46,72). Noncontrast CT usually reveals a homogenous hypodense solid mass extending beyond the pancreas and involving adjacent organs as well as peripancreatic lymph nodes (72). Primary lymphomas of the liver represent only 0.4% of extranodal lymphomas and 0.01% of NHL (47). Most of the few cases reported are diffuse large B-cell lymphomas with other types even rarer; thus, these are expected to be FDG avid (73). Presentation is most commonly in the form of a hypoattenuating solitary lesion. Multiple lesions occur less frequently. A diffuse infiltrating presentation is far more common in secondary involvement of the liver in cases of nodal lymphoma. Rim enhancement can occur in these lesions (74,75).

Secondary involvement of the adrenal gland by NHL can occur in up to 25% of patients. In distinction, primary adrenal lymphoma is extremely rare. Typically, patients with primary adrenal lymphomas present with fever, weight loss, lumbar pain, with or without symptoms of adrenal insufficiency (76). About half the patients will have adrenal insufficiency. Histologically, most are diffuse large B-cell lymphomas (49,50). Adrenal lymphomas are shown to have increased FDG uptake, and on CT they may present as irregular soft tissue masses that enhance heterogeneously or homogeneously. Occasional cystic characteristics and calcification can occur (49,50). Interestingly, these lymphomas are frequently bilateral with a low incidence of extra-adrenal malignancy (49,50).

Primary renal lymphomas are extremely rare, representing approximately 0.7% of extranodal lymphomas, with a majority of patients over 40 years old. Mean age of patients is around 65 years (77). Primary renal lymphomas appear as a distinct renal mass or as an infiltrative process, where it is often bilateral (51). Patients can present with renal failure, which occurs particularly with the diffuse infiltrative form that compresses renal tubules (77). Infiltrative renal lymphomas tend to be diffuse large B-cell lymphomas that are expected to be FDG avid; however, PET identification is hampered by normal renal accumulation of the tracer (Fig. 10). Uptake of FDG in primary renal lymphoma has not been reported.

The overall prognosis for primary renal lymphoma is poor, particularly for bilateral renal disease (77).

Similarly, primary testicular lymphoma is most often a diffuse large B-cell type histology. Follicular lymphomas, lymphoblastic lymphomas, Burkitt, MALT lymphomas, and plasmacytomas have also been reported with primary presentation in the testes (78,79). In men 60 years or older, testicular lymphomas are the most common testicular malignancy. However, overall, testicular lymphoma is relatively uncommon, comprising approximately 1% to 9% of all testicular neoplasms (78). In the immunocompetent population, primary testicular lymphoma occurs more commonly in the elderly, while in the immunosuppressed, younger patients are affected. The incidence is increased in HIV-positive patients (79). Presentation is in the form of a testicular mass, either unilateral or bilateral, which in general is initially assessed by ultrasound. By and large primary testicular lymphomas are aggressive tumors. While many present as stage I, tumors are also diagnosed at advanced stages. Spread occurs to less typical sites such as the CNS in 6% to 16.5% and Waldeyer's ring in 6% at presentation (78). Lung, skin, and contralateral testes are also more common sites of involvement (80). Pulmonary metastases manifest as well-defined nodules. Given its propensity for distant spread, FDG PET/CT clearly has a role in staging. Moreover, the two-year relapse rate is extremely high, making close surveillance by PET/CT an important tool (78).

Primary lymphomas of the female genital tract, including the ovary and uterus, comprise only about 1% of NHL and less than 0.5% of gynecological cancers (81). Patients usually present clinically with fever or night sweats. Histologically, aggressive forms are the most prevalent. The cervix is the most common site of origin. On CT, primary lymphoma of the uterus will present with uniform enlargement of the uterine fundus or mass in the cervix (53). Ovarian lymphoma presents as an adnexal ovarian mass (82). Secondary ovarian involvement by nodal lymphoma is more common than primary ovarian lymphoma (52). Because prognostic factors include Ann Arbor stage and number of sites involved, FDG PET could provide important prognostic and staging information although most patients present in early stages of the disease (53). Patients with primary lymphomas arising in the female genital tract often show prolonged relapse-free survival after combined chemo- and radiotherapy (52,53).

Primary Extranodal Lymphoma of the Lung and Mediastinum (Thymus)

Primary Pulmonary Lymphoma

Primary pulmonary lymphomas comprise less than 1% of all NHL, only 3% to 4% of extranodal NHL, and 0.5% to

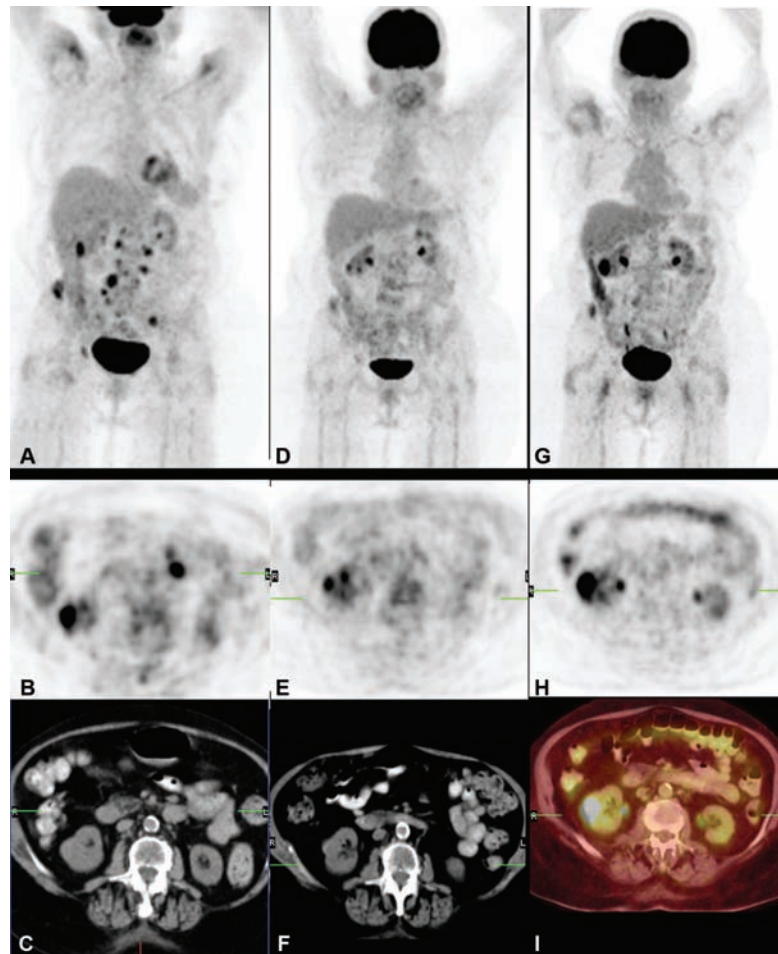


Figure 10 A 58-year-old woman with diffuse large B-cell lymphoma involving both the right kidney, lymph nodes and bone (right iliac crest). Anterior view of the MIP from initial staging FDG PET/CT (**A**) shows the right kidney uptake. Transaxial FDG PET (**B**), and corresponding CT sections (**C**) show the uptake and the right renal mass, respectively. Anterior view of the MIP from FDG PET/CT performed after the completion of chemotherapy (**D**) shows persistent, albeit reduced, metabolic activity in the renal mass. On the transaxial FDG PET (**E**) the uptake in the lateral right kidney is less extensive and on the CT (**F**) the mass is smaller but still present. Anterior view of the MIP FDG PET/CT performed three months later (**G**) shows recrudescence of right renal activity as does the transaxial PET slice through the right renal mass on CT (**H**). The corresponding fused image (**I**) shows that the mass has re-grown.

1% of all pulmonary malignancies (83,84). Primary pulmonary lymphoma is diagnosed when there is clonal lymphoid proliferation affecting the lung parenchyma or bronchi without detectable extrapulmonary involvement at diagnosis and for the subsequent three months (83). Primary pulmonary lymphoma of the lung is most commonly the MALT type (83). The term “pseudolymphoma” in the past referred to these lesions; however, this term has been abandoned given the clonal proliferation that is present (83). These tumors are typically low-grade tumors that arise in bronchus-associated lymphoid tissue (BALT), within follicles that are located along the distal bronchi and bronchioles. Other forms of non-MALT low-grade NHL can occur in less than 10% of cases, with similar behavior

to MALT-type counterparts. High-grade B-cell NHL comprises 11% to 19% of primary pulmonary lymphoma, typically occurring in patients with immunodeficiency such as after organ or marrow transplantation, and they demonstrate more aggressive behavior (83). In the AIDS population, primary pulmonary lymphoma occurs when the CD4+ cell count is typically less than 50/ μ l.

Low-grade primary pulmonary lymphomas on CT most commonly manifest as a solitary, well-circumscribed soft tissue nodule or mass, although multiple nodules also occur (85,86). Air-bronchograms may be evident in these nodules. Peribronchovascular spread and extensive lobar pneumonic-appearing air-space consolidation can also appear (85) (Fig. 11). Suspicion of malignancy is

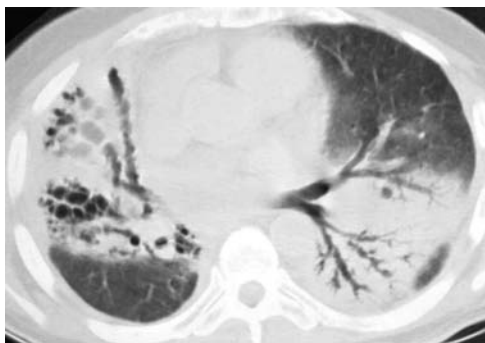


Figure 11 Axial CT section viewed in lung window settings from a 65-year-old male demonstrates diffuse bilateral consolidation representing infiltrative primary pulmonary lymphoma. Cystic and varicose bronchiectasis bilaterally is also present, presumably related to the chronic consolidation.

raised when consolidation is chronic in nature, as typical pneumonic appearing abnormalities of infectious etiologies should clear over a few weeks. Comparison with any prior imaging is, therefore, essential. In a study by Graham et al. of 18 patients with primary pulmonary lymphoma, consolidation or infiltrate was identified in 39%, nodules in 39%, masses in 31%, with bilateral disease occurring in 39% of patients (86). Other etiologies that can produce chronic air-space disease other than primary pulmonary lymphoma are bronchoalveolar carcinoma and inflammatory diseases such as bronchiolitis obliterans organizing pneumonia. Mediastinal lymphadenopathy is identified infrequently on CT with primary pulmonary lymphoma, although nodal involvement has been identified more frequently on pathological analysis in 30% of patients (85). Atelectasis or effusions are uncommon in MALT-type lymphomas (83). High-grade tumors manifest more aggressively with more rapid growth and larger lesions (87).

In AIDS-related primary pulmonary lymphoma, one or multiple nodules or a large mass was described in all of the 12 cases reported by Ray et al., with cavitation occurring in 5 cases (88). It should be noted that secondary involvement of the lung by systemic lymphoma in AIDS is much more common than primary pulmonary lymphoma. Involvement of the lung by systemic lymphoma in AIDS occurs in 70% of cases, and the lung is the most common extranodal site of disease. Nodules are common, particularly on CT, although consolidation and interstitial infiltrates may also be present up to 40% in some series (89,90). Thoracic lymphadenopathy in secondary involvement of the lung was present in 54% of cases (89), although other reports show it to be less frequent (89,90).

Primary Mediastinal Lymphoma

Primary mediastinal or thymic large B-cell lymphoma is a discrete clinico-pathologic subtype of diffuse large cell

lymphoma (91). Primary thymic lymphomas are uncommon and show aggressive although localized behavior (91–94). Reports have also described involvement of the posterior mediastinum (95). A female predominance and a predilection for young adults have been identified (92).

On PET, primary thymic lymphoma will show FDG avidity (96). A lack of other nodal involvement with a large solitary mediastinal mass may raise this entity as a possibility. On CT, these lesions appear as typically low density, lobulated masses that are usually homogeneous on unenhanced imaging but heterogeneously enhance after contrast administration (97). However, necrosis or hemorrhage may cause heterogeneity on noncontrast images. Masses can approach 10 cm or greater in size (94). In one series of 106 cases of primary B-cell lymphoma of the mediastinum by Lazzarino et al., 60% of masses had direct extranodal extension into adjacent structures with pleural and pericardial effusions occurring approximately one-third of the time (94). The differentiation from mediastinal HD, which presents as a large anterior mediastinal mass and confluent adenopathy, is difficult on imaging.

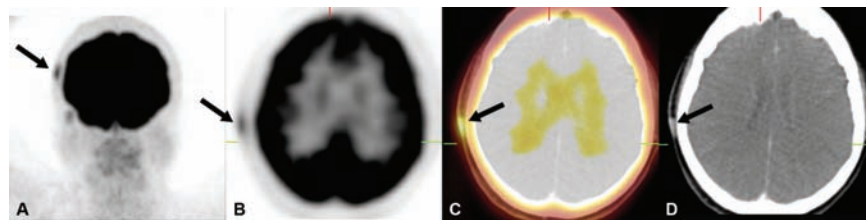
Primary Cutaneous Lymphomas

Primary cutaneous lymphoma is the second most common group of extranodal NHL, after the gastrointestinal system (98). Primary cutaneous T-cell lymphoma comprises a heterogeneous group histologically. The classification of cutaneous lymphomas is in rapid evolution. There are cutaneous T-cell/NK-cell lymphomas, cutaneous B-cell lymphomas, and precursor hematological neoplasm, with the T- and B-cell variants comprising 95% of cutaneous lymphomas (98,99) (Table 4). B-cell lymphomas are less common than their T-cell counterparts, comprising approximately 25% of cutaneous lymphomas. The differentiation of primary cutaneous lymphomas from secondary involvement of the skin by systemic lymphoma is essential, as the two entities have very different prognoses, necessitating exclusion of systemic lymphoma by diagnostic imaging and laboratory tests that include bone marrow biopsy.

Each of the forms of B-cell cutaneous lymphoma has varying presentation and clinical behavior and, therefore, merits brief description. Poorer survival (50%) has been associated with large B-cell (leg type) variant, which presents 10% to 15% of the time involving the skin in areas other than the legs. Multiplicity in the leg-type variant is an adverse risk factor (100). Extracutaneous dissemination is a more common occurrence than in other forms (100). In these patients, FDG PET/CT can provide important staging and follow-up information (Fig. 12). Follicle cell and marginal zone B-cell lymphomas may be multifocal; however, spread to extracutaneous sites is rare

Table 4 Current WHO—European Organization for Research and Treatment of Cancer Classification of Cutaneous Lymphomas

Cutaneous T-cell and NK-cell lymphomas		
Mycosis fungoides Mycosis fungoides variants and subtypes Sézary syndrome Adult T-cell leukemia/lymphoma Primary cutaneous CD30+ lymphoproliferative disorders Subcutaneous panniculitis-like T-cell lymphoma Extranodal NK/T-cell lymphoma, nasal type Primary cutaneous peripheral T-cell lymphoma, unspecified		
Cutaneous B-cell lymphoma	Primary marginal zone B-cell lymphoma	Solitary or multifocal papules plaques or nodules Preferably the trunk or extremities
	Primary cutaneous follicle center lymphoma	Solitary or grouped plaques or tumors Scalp, forehead, trunk, rarely leg
	Primary cutaneous diffuse large B-cell lymphoma, leg type	Red or bluish tumors One or both of the lower legs
	Primary cutaneous diffuse large B-cell lymphoma, other	Rare cases
Precursor hematological neoplasm		
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)		

**Figure 12** A 63-year-old woman with recurrent cutaneous B-cell lymphoma in scalp nodules (*arrows*). Anterior view of an MIP image from an FDG PET/CT (A), transaxial PET slice (B), corresponding fusion (C), and CT (D) with soft tissue windows shows increased FDG tracer fusing to the right-sided subcutaneous scalp nodule.

(100). These two types have a good prognosis after treatment with combinations of surgery, radiation, or chemotherapy, with five-year survival on the order of 95% to 100% (100,101).

Cutaneous T-cell lymphomas include a number of types (99,102) (Table 4). The majority of cases of cutaneous T-cell lymphoma are Mycosis fungoides (103). Mycosis fungoides indolently begins as patches, then forms plaques, and subsequently tumors in the skin. A triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells in the skin, lymph nodes, and peripheral blood are present (98).

Treatment options are palliative and include UV therapy. Lymph nodes and viscera eventually are affected with ultimately rapid progression toward fatal disease (98).

The role of imaging in these lymphomas is to stage extracutaneous disease. FDG PET alone has been reported to have an 82% sensitivity for cutaneous lesions, as compared with the 55% sensitivity of CT (104). For extracutaneous involvement at initial staging, PET had a lower sensitivity of 80% in comparison with CT's 100% sensitivity (104). In that series for restaging patients, PET showed a sensitivity of 86% and a specificity of 92% for cutaneous lesions compared with 50% sensitivity and 83% specificity for CT. In a



Figure 13 A 48-year-old man with recurrent T-cell cutaneous lymphoma. PET/CT was performed for restaging. Anterior view from an MIP (A) shows several foci of uptake at the knee. Sagittal PET (B), fused image (C) and CT (D) show that the foci of uptake correspond to cutaneous nodules. Disease was confined to the lower extremity in this patient.

study by Kumar et al., PET had a 100% accuracy for extracutaneous disease at restaging (104) (Fig. 13).

Primary CNS Lymphoma

Previously associated with immunosuppression, the incidence of primary CNS lymphoma is increasing in immunocompetent patients (105). MRI is the preferred method to diagnose CNS lymphoma but is no more specific than contrast-enhanced CT, which demonstrates single or multiple homogeneously enhancing lesions, often in a periventricular distribution (106). The appearance is indistinguishable from toxoplasmosis.

PET has shown good sensitivity for CNS lymphoma in both immunocompetent and immunosuppressed patients, although it is not the imaging modality of choice for initial diagnosis (Fig. 14). Uptake is usually intense, akin to that of high-grade gliomas (107). Because of the intensity of uptake in these lesions, sensitivity has been limited only by the relatively low-spatial resolution of PET (105). In the immunocompromised population, FDG PET has shown 100% sensitivity in a small series of patients in distinguishing toxoplasmosis from CNS lymphoma (107–109). However, PET may be positive in progressive multifocal

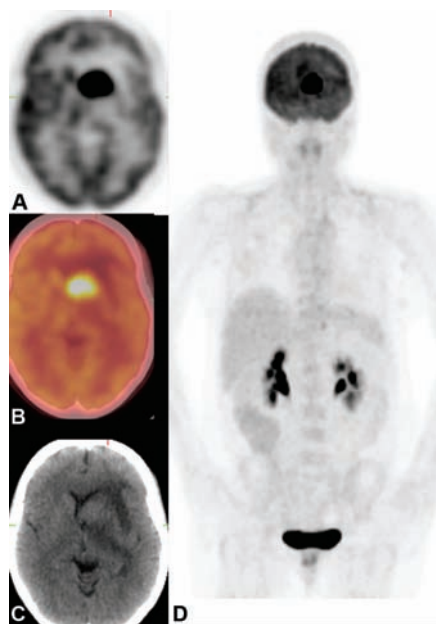


Figure 14 A 67-year-old woman presenting with headache and personality changes. (A) FDG PET transaxial slice shows intense uptake that clearly fuses (B) to the hyperdense mass on CT (C). Surrounding low-attenuation edema is not metabolically active. The anterior MIP view (D) from the whole body FDG PET/CT suggests that there is no other site of disease, which is the usual case in primary CNS lymphoma.

leukoencephalopathy, decreasing its specificity in this group of patients. FDG PET may prove useful for reassessing patients soon after the institution of therapies such as dexamethasone. In particular, changes in kinetic analysis parameters have been identified in patients early during treatment for CNS lymphoma (110). In a study by Palmedo et al., after two cycles of chemotherapy, FDG PET was shown to be more accurate than contrast-enhanced MRI for predicting response (105).

Although response rates to chemotherapy and radiation are high, tumor recurrence is common (111). PET imaging may play a role in the detection of recurrent tumor. In patients treated with radiation, FDG PET has been very accurate for distinguishing between radiation necrosis and tumor recurrence, just as with gliomas (105). ^{11}C methionine PET has also been studied (112). Sensitivity may be limited by spatial resolution, but the positive predictive value of PET in general is expected to be high (109).

Primary dural lymphoma is exceedingly rare and presents as an extra-axial enhancing mass. The usual histology is marginal zone lymphoma of the MALT type. MRI as a primary means of imaging is preferred. While similar to a meningioma in appearance, the presence of brain invasion and vasogenic edema may raise

suspicion of lymphoma. Although likely to be FDG avid, the main role of FDG PET is to identify extracranial disease (58). Although the primary tumor responds well to radiation, the risk for systemic relapse is high (58).

Primary intraocular lymphoma involves the vitreous or retina. The cell type is usually a diffuse large B-cell lymphoma of high-grade malignancy (113). In a large number of patients, the lymphoma will extend from the retina into the more central CNS. Eighty percent of cases are bilateral (114). Systemic dissemination is rare, although the prognosis is usually poor (113). Ultrasound and fluorescein angiography are the primary imaging modalities for diagnosis, but because of the frequent CNS involvement, brain MRI is an important adjunct. FDG PET has not played any significant role in primary intraocular lymphoma because of the usually small size of the lesion (59,114).

PROGNOSTIC VALUE OF SUV AT STAGING

For HD, the number of involved regions, the presence of B symptoms, extranodal or bulky disease, age, blood counts, all help predict survival. While CT has been the standard, it has been suggested that PET may be useful. The intensity of FDG uptake may correlate with patient prognosis (115) and FDG PET has higher sensitivity for detecting some sites of disease, for instance in the abdomen (35).

Early studies suggested that high SUVs would be found in high-grade NHL, low SUVs in indolent lymphoma, and intermediate values in transformed low-grade lymphomas (116). In a fairly large series of patients, SUVs of indolent and aggressive lymphomas showed overlap, but aggressive lymphomas could be distinguished by SUVs greater than 10, yielding a specificity for aggressive disease of 81% as compared with indolent lymphoma (117). Also, SUVs tended to correlate with histologic grade of NHL and proliferative indices (118). However, other authors have found no difference in SUV between different grades of tumor and wide variation among lesions within a single patient (16). This issue remains unsettled.

The sensitivity of FDG uptake, not surprisingly, may vary depending upon histologic type. FDG PET is highly sensitive (98–100%) in patients with HD, diffuse large B-cell lymphoma, mantle cell and follicular lymphomas, regardless of grade (30,40,119). FDG uptake is high even for low-grade follicular lymphoma, the most common indolent form of NHL (30). PET demonstrates lower, but moderate sensitivities for marginal zone lymphoma (71%) and peripheral T-cell lymphomas (30,40,120). PET for low-grade small cell lymphocytic lymphomas/chronic lymphocytic leukemias has even lower sensitivities on the order of 53%, underestimates extent of disease, and underperforms CT for staging (30,41). With the addition of CT

information provided by PET/CT, the mild uptake in lymph nodes associated with small cell lymphocytic and chronic lymphocytic leukemia cell types is more readily identifiable as adenopathy (Fig. 8). Interestingly, it has been suggested that increased SUV in patients with CLL greater than 5 may portend a Richter's transformation to diffuse large cell lymphoma or other lymphomas (121).

PET/CT FOR PREDICTING OUTCOME

Early Reassessment

Early follow-up of lymphoma with PET has been found to be useful in predicting outcome and in identifying patients who require more aggressive therapy (116). Early reassessment has been primarily studied very early on after initiation of therapy at one week or after two to three cycles of chemotherapy.

Experimental studies have shown that FDG uptake in lymphoma generally correlates with the number of viable tumor cells. Conversely, investigators have supported the ability of PET to image "tumor stunning." In an in vitro study using etoposide on Hodgkin's lymphoma, the investigators demonstrated that viable cells showed decreased deoxyglucose uptake suggestive of tumor stunning (122). This may explain that FDG PET performed in patients at one week after the institution of therapy, when "stunning" may be an issue, will show a decrease in uptake by lesions; FDG PET performed at six weeks after the institution of therapy, at least in patients with NHL will be more reliable (123). Also, in this study, Patlak analysis of FDG uptake kinetics for tumor was more reliable than simple SUV analysis. In another group of patients with either NHL or HD, negative FDG uptake after one cycle of chemotherapy was more predictive of a relapse-free outcome [83% negative predictive value (NPV)] than at the end of chemotherapy (61% NPV). Positive FDG studies after one chemotherapy cycle also had a 90% positive predictive value for poor response (124). In a group of 108 patients with HD, FDG PET after two courses of chemotherapy was 95% accurate in detecting still-viable disease and highly predictive of disease-free survival over two years, (96% for those with negative and 6% for those with positive PET scans) (125). In this study, FDG PET after two cycles of chemotherapy had independent prognostic value beyond the initial clinical stage at diagnosis (125) (Fig. 3).

Repeatedly, FDG PET studies have shown an excellent prognostic value for a negative PET and a poor prognostic indication of a positive PET after two to three cycles of chemotherapy. Positive FDG PET after three cycles of chemotherapy predicted a 0% disease-free two-year survival, but negative PET patients had complete remissions

at the end of therapy and a 62% relapse-free two-year survival in a series of NHL patients (126) (Fig. 10). In a small group of patients with high-grade lymphoma studied after two to three cycles of chemotherapy, any abnormal uptake predicted a relapse in 88% of patients. Patients without uptake at that point in treatment did not relapse over a 30-month follow-up period (127). Haioun et al. showed that negative FDG PET after two cycles of chemotherapy was associated with a complete response after four cycles and prolonged survival in patients with NHL, primarily diffuse large B-cell lymphoma (128). In this series a positive PET after two cycles correlated with a poorer complete response rate after completion of chemotherapy (58%) and a 39% disease-free survival (128).

Prognostically, on PET performed at the completion of therapy in a group of patients with either non-Hodgkin's or Hodgkin's lymphoma, the presence of FDG activity in residual CT abnormalities had a 68% positive predictive value for recurrence within four years (129) and a 96% NPV. This has held true even in the setting of residual bulky disease (130). Qualitative assessment appears to be as accurate, or even more so, than analysis of SUV changes (125).

In distinction, early assessment in children with PET may be less helpful. In one series, a negative FDG PET after two to four cycles of chemotherapy had only a moderately high NPV (84%) with all the false negatives occurring in the setting of NHL (11). In a group of children and adolescents, two-thirds of whom had HD and the remaining with NHL, PET/CT performed after one or two cycles of chemotherapy demonstrated a high (95%) NPV (12). Therefore, it has been suggested that the earlier assessment after only one cycle of chemotherapy may be accurate for predicting outcome (11). However, negative end of therapy PET/CT was shown to have a more uniformly high NPV for relapse-free survival (11,12). Thus, the value of early FDG PET in the pediatric age group is not clearly established, and end of therapy PET (and, likely, PET/CT) adds important prognostic information.

Identifying Populations for Bone Marrow Transplantation

Imaging may be used to identify chemosensitive patients who are more likely to benefit from aggressive and sometimes morbid bone marrow transplantation (131). PET performed after induction chemotherapy prior to autologous stem cell transplantation has been shown to predict disease-free survival after transplantation (132). This is true of CT as well, but CT may be less accurate because of residual masses after therapy (132). Prior to transplantation, a positive FDG PET after induction chemotherapy is highly specific for progression and has a high positive predictive value persistent or recurrent

disease (133). In a series of patients scanned at the end of chemotherapy prior to transplantation, a negative FDG PET had an 83% positive predictive value for prolonged overall survival and a positive PET was associated with relapse in 87% after transplantation (134).

PET done earlier, i.e., after two cycles of induction chemotherapy prior to transplantation may also add value. Schot et al. reported that a PET study performed at this point in therapy will predict a two-year disease-free survival after transplantation, if negative, in 71% and a rapid relapse, if positive (131). Cremerius et al. showed that a reduction in metabolic activity by greater than 25% of the SUV between PET scans obtained after two cycles and at the end of chemotherapy carried a much better prognosis for overall and disease-free survival posttransplant than in patients whose tumor SUVs declined by less than 25%. No relationship between baseline uptake and eventual outcome was demonstrated (133).

RESTAGING AFTER THERAPY

CT scan assessment of lymphoma combined with clinical evaluation, laboratory blood tests, and bone marrow biopsy make up the traditional means of assessing treatment response according to the International Workshop Criteria (IWC) (Table 5).

More recently, it has been suggested that PET be incorporated into the measurement of treatment response for NHL (135). In HD, restaging typically occurs between chemotherapy and radiation therapy. In NHL the timing for restaging is more variable.

In restaging of lymphomas in general after chemotherapy, PET, and increasingly PET/CT have shown greater accuracy, sensitivity, and specificity (31,136) than CT alone. In one series, sensitivity was 96% for PET alone versus 38% for CT (137). More recently, Schaefer et al. reported 85% sensitivity for PET/CT for lymph nodes and 100% sensitivity for extranodal disease (31) compared with 69% sensitivity for lymph nodes and 75% sensitivity for organ involvement with CT alone. PET has been reported to be falsely negative at restaging in a number of sites, all lymph nodes (13), and comparison and consideration of the CT findings must be made with close follow-up.

The benefit of interpreting PET in conjunction with CT has been shown. In a group of 27 patients with lymphoma where CT had a sensitivity of 78% and specificity of 54%, correctly staging 67%, PET alone showed a sensitivity of 86% and specificity of 100%, correctly staging 93%. When combined by either side-by-side readings or fused studies of PET and CT, these numbers improve to 93% sensitivity, 100% specificity, and correct staging in 96% (138). PET/CT downstaged over a quarter of the patients compared with CT staging and upstaged a comparable

Table 5 Criteria for Treatment Response in NHL, IWC vs. IWC plus PET

Response	IWC criteria	IWC and PET criteria
CR	Normalization of all sx and biochem. abnorm.; normal BM; decrease to <1.5 cm all masses previously larger; decrease to <1.0 cm all masses up to 1.5 cm	–IWC CR and neg. PET; –IWC CRu, PR, or SD and neg. PET and BM; –IWC PD but neg. PET and nl BM
CRu	Normalization of sx and biochem. abnorm.; residual mass >1.5 cm decreased by 75% or indeterminate BM bx	CR by IWC, neg. PET, and indeterminate BM
PR	≥50% decrease in SPD of 6 largest lymph nodes or masses without evidence of new sites or any progression	–IWC CR, CRu, PR with pos. PET at site of prior disease; –IWC CR, CRu, PR, or SD with pos. PET at new site –IWC SD with pos. PET at previously enlarged node now decreased in size
SD	Less change than PR, but no evidence of progression	IWC SD with pos. PET at prior site of disease
PD	≥50% increase in SPD of previous known abn, new lesion during or at end of therapy	–IWC PD with pos. PET –IWC PD, neg. PET, new or enlarging CT abnormality <1.5 cm or <1.0 cm in lungs

Abbreviations: IWC, international workshop criteria; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SPD, sum of the product of greatest diameters; SD, stable disease; PD, progressive disease; sx, symptoms; biochem., biochemical; abnorm., abnormalities; BM, bone marrow; neg., negative; pos., positive; nl, normal; bx, biopsy.

Source: From Ref. 135.

number. PET/CT changed staging in three patients compared with PET alone in that series (138). In a group of pediatric patients, PET was positive in only 14% of the residual masses on CT. While CT had a positive predictive value of 14%, PET/CT correctly predicted residual disease when there was corresponding, heterogeneously increased uptake (12).

In the majority of patients being restaged, there will be complete concordance between PET and CT (139). Discordant results between PET and CT occur when persistently enlarged nodes on CT demonstrate absent or at least markedly decreased FDG accumulation (13,137). The evaluation of residual mass using FDG PET now has recognized value both in adults and children (6,12,139). Two-third to four-fifth of patients with HD and 40% of NHL patients will show residual abnormality on CT after therapy, but only about a quarter of these will eventually relapse (129,135,139).

Residual mass on CT should be considered truly negative when corresponding to “cold” areas on PET. In a meta-analysis of 723 patients, the sensitivity of PET ranged from 79% to 100% and the specificity from 69% to 100% (140). The NPV of PET in the setting of residual mass on CT in HD is high, reportedly 81% to 100%; but the positive predictive value for the presence of active disease is less, 19% to 60% (139,140) (Fig. 3). The lower positive predictive value is related to false positives after chemotherapy secondary to thymic hyperplasia and, if performed after radiation therapy, inflammatory change that occurs up to three months after radiation therapy but may persist for an even longer period of time. If PET is

interpreted with consideration of known sites of previous disease and in the setting of significant clinical history, the positive predictive value for both HD and NHL rises to probably 80% (139).

This holds true not only after first line therapy, but also in patients undergoing salvage chemotherapy prior to stem cell transplant. A positive PET portends a poor outcome for these patients. A negative PET in spite of residual CT abnormality correlates with a good outcome posttransplant (141). Finally, a mixed response of progression and regression documented by PET portends a very poor prognosis (142). Overall, the sensitivity and specificity of FDG PET alone for residual HD at the completion of therapy is 84% and 90%, respectively. For NHL, sensitivity and specificity of FDG PET is 72% and 100%, respectively (143).

Prognostic Information at Restaging

Restaging at the conclusion of therapy offers prognostic information (Table 6). In bulky abdominal disease, either

Table 6 PET or PET/CT in Assessing Patients After Therapy: Relapse Rate

Authors (Ref.)	PET+	PET–
Zinzani et al. (144)	100% (CT+); 96% (CT–)	0%
Mikhael et al. (127)	100%	17%
Juweid et al. (145)	92%	12%
Jerusalem et al. (146)	100%	10%
Filmont et al. (136)	79%	—

HD or aggressive NHL, a negative PET and CT predicts a relapse-free survival, a negative PET with residual abnormality on CT predicts a low incidence of relapse, but a positive PET predicts relapse in 100% of patients within two years (144).

In high-grade NHL, a negative PET at the conclusion of chemotherapy was associated with a 17% relapse rate compared with 100% for positive PET studies. PET was more accurate than CT with a positive CT associated with relapse in only about 40% of patients (127). In another group of high-grade NHL patients, only 3 of 25 patients with negative PETs at the conclusion of chemotherapy relapsed while 92% of patients with positive PET studies relapsed within 26 months (145). In a mixed group of HD and intermediate or high-grade NHL patients, a positive PET at restaging predicted relapse in 100% of patients compared with residual mass on CT, which predicted relapse in only 42% of patients. In that series a negative CT and PET was associated with a 10% relapse rate (146).

In HD, at a median time point of 5.2 months after the completion of therapy, PET had a predictive accuracy of 91%, a positive predictive value for relapse of 79% in a study by Filmont et al. (136). Disease-free survival throughout follow-up was predicted by a negative PET in HD, where conventional imaging (including CT) was not (136).

The addition of PET to restaging may improve categorization of overall response to therapy and better predict prognosis (Table 5). In a study by Juweid et al., when comparing the IWC response assessment algorithm with the IWC plus PET algorithm in NHL, 39% of the patients had discordant response status. In a majority of cases, the incorporation of FDG PET into the IWC response algorithm led to a more favorable response category (135). The three most common recategorizations that occurred with the addition PET to IWC, were: (1) Cru (complete response, unconfirmed) to CR (complete response), (2) Cru to PR (partial response), and (3) PR to CR. In these instances, patient outcomes supported the accuracy of the recategorization using PET data. Patients with CR by IWC criteria alone had similar survivals to those with CR by IWC plus PET criteria (135). However, the patients with PR by IWC plus PET criteria had a worse progression-free survival than those with PR by IWC criteria alone. This was largely due to the inclusion of PET-positive patients in the classic IWC classification.

Restaging in the Pediatric Age Group

In children also, FDG PET in concert with CT has shown a 76% to 80% positive predictive value in assessing a complete response to therapy (6,147) with a much lower positive predictive value using CT alone and a consistently

high NPV for both PET and CT (6,147). Furthermore, once a negative PET is achieved in children after therapy, a negative PET/CT, even when the CT may show residual soft tissue abnormality, offers a very high NPV for recurrent disease (148). In this population, sensitivity and specificity of PET for recurrence is high, 95% and 90%, respectively.

False positives are most frequently caused by lymphoid hyperplasia and thymic rebound/hyperplasia. Because of those false positives, the positive predictive value is only about 53% (148). Because PET activity reverts to normal long before CT, recurrent activity on PET, rather than persistent soft tissue abnormality on CT, e.g., enlarged lymph nodes, may confound interpretation or even mask recurrences. PET has been shown to have a 100% NPV in CT-persistent mediastinal masses with a high recurrence rate in patients who had persistent FDG uptake in those masses (149). Although false positives outside the mediastinum have been reported in up to 55% of the patients with PET alone (150), in-line PET/CT is expected to reduce this by clarifying the presence of uptake in brown fat, muscles, and even ureters, rather than lymphomatous tissue. PET alone will influence a change in management in the setting of monitoring.

NONMALIGNANT LYMPHADENOPATHY AND PET/CT IMAGING

A number of pathologic syndromes may mimic lymphoma on the basis of lymphadenopathy and clinical symptoms (Table 7). Many of these entities will present with increased uptake on FDG PET. Depending upon the pathologic activity of these non-neoplastic diseases, uptake can range from negligible to extremely high. Therefore, PET's role in differentiating forms of adenopathy is limited. In many cases, scrutiny of the clinical history and/or tissue diagnosis will be necessary to confirm the absence of lymphoma. However, when used in

Table 7 Nonlymphomatous Causes of Diffuse FDG-avid Lymphadenopathy

Tuberculosis (202)
Sarcoidosis (157)
HIV-related adenopathy (155,156)
Infectious mononucleosis (153)
ALPS (179)
Amyloidosis (203)
Rosai-Dorfman syndrome (204)
Systemic lupus erythematosus (176)
Chronic lymphocytic leukemia (121)

References are cited in parentheses.
Abbreviation: ALPS, autoimmune lymphoproliferative syndrome.

conjunction with the CT characteristics, PET/CT has a greater ability to narrow the differential diagnosis. Additionally, nonpathologic FDG uptake in brown fat can usually be identified definitively by fused PET and CT images (13).

Assessment of Lymphadenopathy on CT

On CT, lymphadenopathy is present in a number of disease states. The differential diagnosis for lymphadenopathy includes primary and metastatic neoplasia other than lymphoma, infectious etiologies, pneumoconiosis, Castleman's disease, and inflammatory processes such as sarcoidosis and systemic lupus erythematosus (SLE). Lymph node enlargement can also occur when there is a diffuse or significant intraparenchymal process such as an interstitial pneumonitis, severe bacterial infection with or without abscess formation, hemorrhage, and congestive heart failure. Thus, scrutiny of the lung parenchyma and consideration of "reactive" enlargement of lymph nodes should be considered, particularly when the enlarged lymph nodes lie along the expected distribution of lymphatic drainage from the affected lung regions. Distribution of lymphadenopathy may be helpful, e.g., when lymphadenopathy affects both the right and left sides of the mediastinum and hila symmetrically, particularly when accompanied by a diffuse nodular pattern in the lungs in a perilymphatic distribution that is characteristic for sarcoidosis. A majority of times, however, such a pattern of lymphadenopathy cannot be identified.

Calcifications in nodes are typically related to granulomatous disease such as tuberculosis, sarcoidosis, or silicosis. Lymphoma after treatment can calcify, but rarely before treatment. Additionally, enlargement of nodes may be unrelated to the cause of nodal calcification. Low-attenuation nodes with peripheral enhancement after contrast administration have been described in cases of tuberculous adenitis (151). Malignant lymphadenopathy however may enhance peripherally (152).

Infection

Granulomatous diseases such as tuberculosis, atypical mycobacterial disease, and histoplasmosis are frequently complicated by lymphadenopathy. Uptake on PET imaging can occur in sites of *Mycobacterium tuberculosis* infection. Frequently, elderly patients with evidence of prior granulomatous disease (e.g., calcified mediastinal or hilar lymph nodes, calcified granulomas in lung, liver, or spleen) will present on FDG with bilateral hilar uptake with variable intensity and in normal sized nodes. Diffuse lymphadenopathy

can occur with other infections such as Epstein-Barr Virus (EBV) in infectious mononucleosis (153), in addition to less common infectious entities such as cat-scratch fever caused by *Bartonella henselae* (154).

More problematic is the diffuse lymphadenopathy related to HIV infection. In the United States, uptake in these lymph nodes is usually low level, especially with the use of highly active anti-retroviral therapy (HAART) (155,156) (Fig. 15). However, lymph node uptake may be intense in untreated HIV. Lymph node uptake on FDG PET correlates both with viral load and with the institution and/or withdrawal of HAART (155).

Inflammatory and Other Etiologies

Sarcoidosis is a granulomatous disease characterized by noncaseating granulomas. FDG uptake on PET has been reported frequently in sarcoidosis (157,158). Uptake will respond to treatment of sarcoidosis with steroids (157,159,160). On PET/CT, the classic pattern of bilateral hilar with right paratracheal uptake correlating with enlarged lymph nodes should raise a suspicion of sarcoid. Perilymphatic distribution is suggested when nodular densities are aligned along the pleural, fissural, and peribronchovascular structures (161) (Fig. 16). Correlation with clinical data such as elevated angiotensin-converting enzyme levels and other corroborating clinical manifestations contribute to this entity's diagnosis. Extensive mediastinal lymph node, lung, bone, and other organ uptake can occur (160,162,163). FDG uptake in cardiac, cerebral, and renal sarcoidosis has been reported (164–166).

A sarcoid-like reaction in lymph nodes can occur in patients with malignancy, thereby complicating the management of these patients (167–169). The sarcoid-like reaction is felt to represent an immune response to tumor antigens and may occur in 13.8% of patients with HD, 7.3% of those with NHL, and 4.4% of patients with carcinomas (168) (Fig. 17). In addition, sarcoidosis has been noted with some frequency after chemotherapy for lymphoma (170–172), radiation therapy for squamous cell carcinoma of the tongue (158), treatment of testicular cancer (167), and after alpha-interferon therapy for renal cell carcinoma (Fig. 18) and for hepatitis C (173) (174). Biopsy of these abnormal lymph nodes may be critical for further management of patients with worsening adenopathy after treatment for lymphoma (172). While cytology may be adequate for positive identification of tumor, specific diagnosis of sarcoidosis may require histological evaluation of biopsy specimens (175).

FDG uptake in lymph nodes can occur in SLE (176). It has been suggested that SLE is associated with an increased incidence of NHL and, therefore, may be difficult to

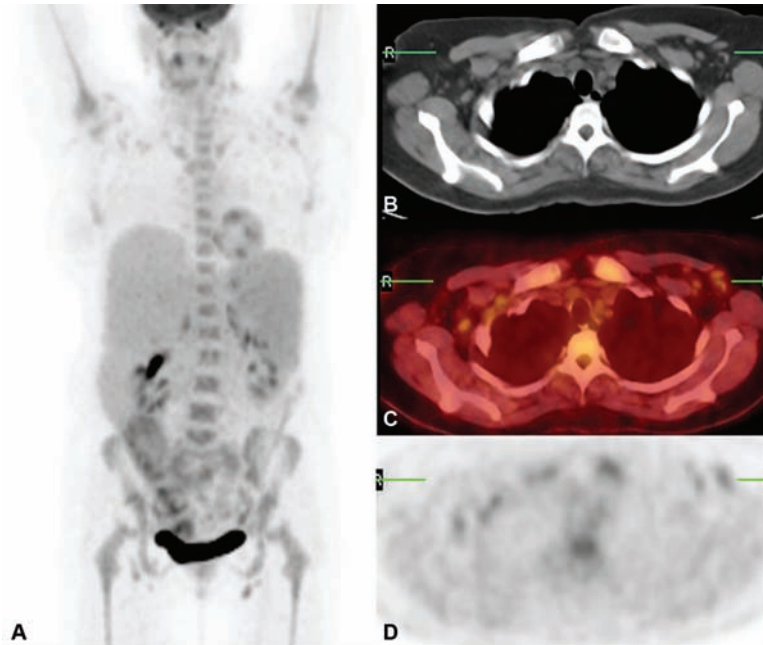


Figure 15 A 46-year-old HIV positive woman on retroviral therapy had a previous history of NHL that was in remission for two years. Anterior view of an MIP from an FDG PET/CT (A) performed for monitoring for possible recurrence shows mild uptake in both axillae, the neck, and both inguinal regions. Transaxial images from corresponding CT (B), PET/CT fusion (C), and PET (D) images show that the mild uptake in the axillae fuses to small but solid appearing lymph nodes. Biopsy subsequently identified inflammatory change consistent with HIV lymphadenopathy, but no lymphoma. The high-grade lymphomas that are associated with AIDS are expected to show intense uptake of FDG. *Abbreviation:* NHL, non-Hodgkin's lymphoma.



Figure 16 A 55-year-old male evaluated by FDG PET and then diagnostic chest CT for lymphadenopathy and suspected lymphoma. The PET study showed bilateral mild hilar and mediastinal lymph node uptake (not shown). High resolution sections obtained as part of a chest CT obtained two weeks later demonstrates peribronchovascular soft tissue (arrow) with multiple nodules predominantly clustered along the centrilobular structures and in the perifissural and subpleural regions suggestive of a perilymphatic distribution. Noncaseating granulomas in a peribronchial location were confirmed by subsequent transbronchial biopsy of the lung.

differentiate nodes related to SLE from lymphoma (177,178). Autoimmune lymphoproliferative syndrome (ALPS) is a syndrome characterized by mutations that impair lymphocyte apoptosis proteins. Patients with ALPS have chronic, but fluctuating, lymphadenopathy in addition to autoimmune-based cytopenias, hepatosplenomegaly, and an expanded population of T-cells that lack both CD4 and CD8 markers (179). SLE has been reported in association with ALPS. There is also an increased risk of lymphoma. Lymphadenopathy in SLE tends to be FDG avid, and PET cannot be used to differentiate ALPS lymphadenopathy or the lymphadenopathy of SLE from lymphoma that may also occur in these patients.

Similarly, Sjogren's syndrome, an autoimmune disease manifesting typically as xerostomia and keratoconjunctivitis sicca may present with lymphadenopathy. Approximately 4% to 8% of patients with Sjogren's syndrome develop lymphoma. The disease has an associated risk of lymphoma that is 44 times the incidence of a normal population (180). Lymphomas tend to be B-cell in origin, of low or intermediate grade, of extranodal origin, typically arising from MALT tissue, although high-grade

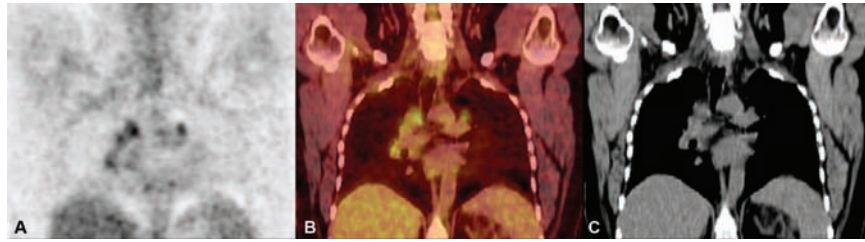


Figure 17 This 45-year-old woman with breast cancer had been treated with chemotherapy in the adjuvant setting. She underwent this FDG PET/CT after completion of the chemotherapy. The clinical setting and the new uptake pattern on coronal PET (A), fused (B), and CT images (C) both suggested that the bilateral hilar and extensive mediastinal uptake were not secondary to her breast cancer. Biopsy showed noncaseating granulomatous disease.

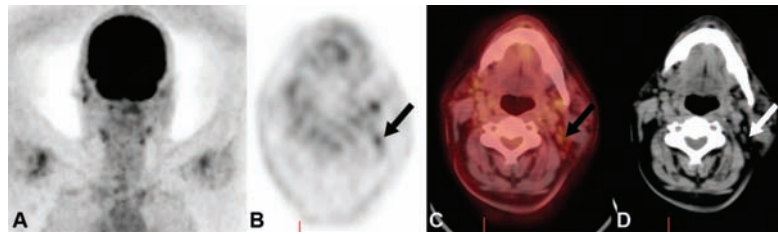


Figure 18 A 49-year-old man with a history of renal cell carcinoma being treated with alpha interferon. Anterior view of an MIP image from an FDG PET/CT (A) performed to evaluate for metastatic disease shows mild bilateral lymph node uptake. Transaxial PET (B), corresponding fusion (C), and CT (D) images shows focal FDG uptake corresponding to a few of the numerous, but unenlarged, left-sided level II lymph nodes (arrows) in the neck identified on CT scan. Biopsy revealed noncaseating granulomas.

large-B cell lymphomas can occur (181). Sjogren's syndrome patients have a well established association with lymphocytic interstitial pneumonitis. Other interstitial lung diseases have also been described (183).

Mesenteric lipodystrophy, a benign condition is sometimes difficult to differentiate on CT or even FDG PET from mesenteric lymphadenopathy secondary to lymphoma. Mesenteric lipodystrophy is less diffuse in nature, stable over time, and occurs in asymptomatic patients. FDG PET is likely to be metabolically negative or only minimally active in stable mesenteric lipodystrophy. CT images will show a well-defined, heterogeneous, fat-density mass in the small bowel mesentery often encapsulated by a thin pseudocapsule (184). In contrast, with lymphomatous involvement of the mesentery, more distinct uptake will be seen associated with the lymph nodes (Fig. 7).

Miscellaneous Lymphoproliferative Disorders

Castleman's disease, also known as angiomatous lymphoid hamartoma or giant lymph node hyperplasia, generally occurs in the typical locations for lymphoid tissue, although most commonly is identified in the thorax up to 70% of the time, neck 20%, and abdomen (10%) (185). Castleman's disease typically affects individuals in the

fourth and fifth decades, although the patient age is younger in the HIV population. Castleman's disease has been separated into localized and multicentric forms. Histologically, there are hyaline vascular forms, comprising 90% of localized Castleman's disease, and plasma cell variants, identified in 80% to 90% of multicentric disease (185). The localized form presents on CT as an enhancing, well-circumscribed mass, which can show low or increased FDG uptake (186,187). Multicentric Castleman's disease involves multiple organs, lymph nodes, and is accompanied by systemic symptoms. Multicentric Castleman's disease is more common in HIV-positive individuals than those without HIV infection. A response to chronic antigen stimulation is believed to play a major role in the development of multicentric Castleman's disease (188). Human herpes virus 8 has been associated with HIV-related multicentric Castleman's disease in all cases (188). Therapies in the non-HIV population are similar to those for lymphoma, while HIV-related Castleman's disease treatments include HAART, antiviral therapy, and immunotherapy such as alpha interferon (185).

Diffuse lymphoid hyperplasia occurs in the gastrointestinal tract and lung. In the lung, the process may be located primarily in the parenchyma, termed lymphocytic interstitial pneumonitis, or be concentrated around the

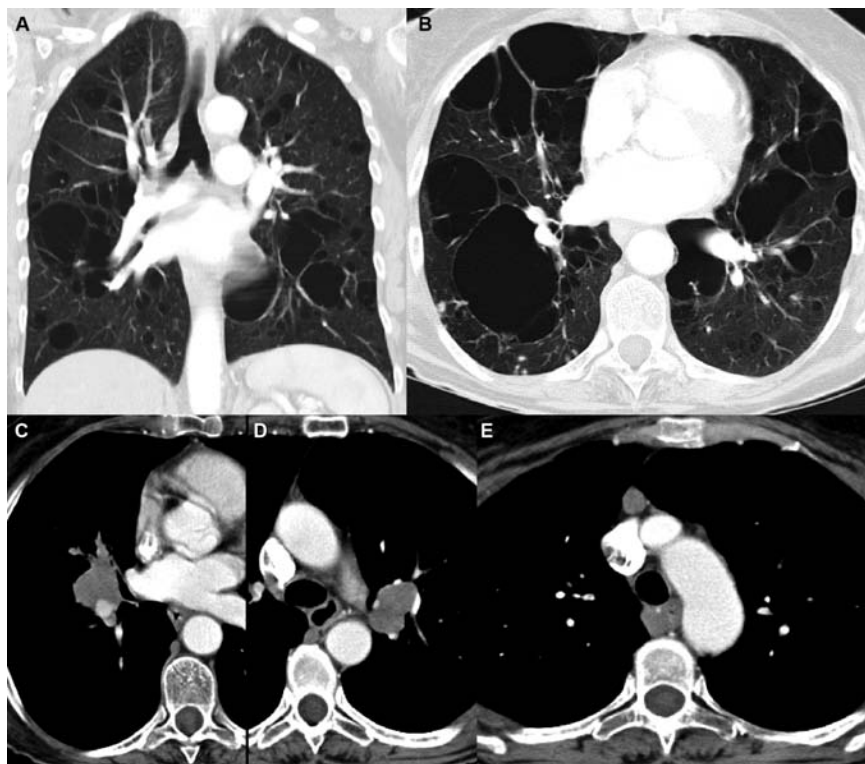


Figure 19 Lymphocytic interstitial pneumonitis and lymphoma. A 64-year-old female with a history of Sjogren's syndrome with lymphoma, underwent chest CT which revealed large scattered cysts of varying size, as best shown on coronal 5 mm MPR (A) and associated small nodules as shown on axial 5 mm section (B) characteristic of lymphocytic interstitial pneumonitis associated with Sjogren's syndrome. The patient five months prior had a CT scan demonstrating adenopathy consistent with lymphoma in the left (C) and right hilar (D) regions and anterior mediastinum (E). Patients with Sjogren's disease are at higher risk of developing lymphoma. *Abbreviation:* MPR, multiplanar reconstruction.

airways. These entities may be related, given similar patient demographics.

Lymphocytic interstitial pneumonitis (Fig. 19) occurs when there is diffuse proliferation of small lymphocytes and plasma cells in the interstitium. An association with autoimmune disease, primarily Sjogren's syndrome or AIDS has been established (182). Lymphocytic interstitial pneumonitis manifests in the lung parenchyma as well-defined scattered cysts typically associated with small poorly-defined nodules and ground-glass opacification (182). There is a perilymphatic distribution, in that the process affects the interstitium surrounding the broncho-vascular bundles, pleura, and septa. Interlobular septal thickening can be identified in 82% of cases (182). Although not as evident on chest radiography, lymphadenopathy was present in a study by Johkoh et al. on CT in 68% of their patients, although the lymphadenopathy may have been related to coexistent disease processes such as Castleman's disease and AIDS. In their 22 patients also, 68% had cysts ranging from 1 to 30 mm in diameter that were distributed randomly and involved less than

10% of the lung parenchyma (189). Cysts can develop from areas involved by nodular densities (190).

Follicular bronchiolitis is lymphoid hyperplasia of the bronchus-associated lymphoid tissue (BALT). Also associated with Sjogren's syndrome and immunodeficiency, follicular bronchiolitis on histopathology has a peribronchial location, although there is overlap with lymphocytic interstitial pneumonitis. In follicular bronchiolitis, the hyperplastic follicles follow the course of the bronchioles. Nodular densities were present in a series of 12 patients reported by Howling et al. with the nodules small, on the order of 3 mm or less, with 42% of patients having nodules between 3 and 10 mm. The nodules were in a centrilobular and peribronchiolar distribution (191).

Lymphomatoid granulomatosis has also been called angiocentric lymphoma and angiocentric immunoproliferative lesion. The entity is characterized a lymphocytic infiltrate that is angiocentric and angi destructive with atypical lymphoid cells (192). Lymphomatoid granulomatosis is currently felt to be an EBV-related T-cell rich B-cell lymphoproliferative disorder. Three grades exist,



Figure 20 Lymphomatoid granulomatosis. coronal MPR demonstrates nodular density with air-bronchograms through the center of the nodule. Other similar nodular densities were present in the lung parenchyma and were centered around the bronchovascular structures, consistent with the disease's bronchocentric nature. *Abbreviation:* MPR, multiplanar reconstruction.

with grade III considered a subtype of diffuse large B-cell lymphoma (193). Diagnosis typically requires surgical lung biopsy, although less invasive biopsy methods can make the diagnosis occasionally. Etiology of lymphomatoid granulomatosis is not clear. Associations with EBV, abnormalities in cell-mediated immunity, and drug-related immunosuppression have been noted (192). Multiple organs can be affected, such as the lungs, CNS, skin, abdomen, eyes, kidneys, and heart (194). In the lungs, peribronchovascular nodular densities are the most frequent features of lymphomatoid granulomatosis (Fig. 20) (195). Coarse irregular opacities along the bronchovascular bundles coexistent with distortion of the architecture of the bronchovascular bundles and small nodules have been reported (195). Large masses, multifocal air-space opacities with or without cavitation, and obstruction of vessels can occur (195,196). Thin-walled cysts have been reported (195). On imaging, therefore, this entity is difficult to differentiate from lymphoma or other lymphoproliferative lung disorders. Treatment may require steroids and combination chemotherapy; and more recently, interferon alpha-2b has been studied (193).

SUMMARY

While histologic evaluation is essential for diagnosing the type of lymphoma and subsequent management decisions, accurate staging relies on imaging. This is particularly important in the pediatric age group where staging will strongly influence the extent of chemotherapy and radiation since efforts are made to limit chemotherapy and radiation to diminish subsequent long-term sequelae of these treatments.

Current state-of-the-art practice supports the use of FDG PET/CT to identify the extent of lymphadenopathy and extranodal disease. While focal uptake on FDG PET in bone marrow should suggest bone marrow involvement regardless of bone marrow biopsy results, a negative FDG PET does not exclude marrow lymphoma. Usually PET and CT results will identify the extent of disease concordantly, but discrepancies do occur that sometimes can only be resolved by close follow-up. Criteria for positive lymph nodes include enlargement on CT, increased FDG uptake in enlarged nodes, and increased uptake in normal sized lymph nodes. More controversial is the intensity of uptake required to determine PET positivity. FDG PET alone has been shown to increase sensitivity over CT alone in initial staging of the spleen and lymph nodes, but CT is more sensitive for pulmonary involvement. PET/CT clearly improves over each single modality for extranodal disease and probably for nodal disease as well, in terms of sensitivity and specificity. PET tends to be sensitive for most primary extranodal lymphomas but its utility in staging and clinical management depends on the degree of dissemination of these primary lymphomas.

FDG PET also provides prognostic information. Even in HD where the extent of disease and clinical attributes are well-accepted predictors of outcome, SUV at diagnosis may predict outcome.

PET/CT plays an important role in early restaging, where the absence of activity after one to three cycles of chemotherapy will predict longer disease free survival. Positive FDG PET portends recurrence. Similarly, PET/CT outcomes during induction chemotherapy prior to bone marrow transplant provide prognostic information. At the end of therapy, PET and PET/CT will predict the outcome in adult patients. This outcome is particularly important in the setting of residual mass on CT. The use of FDG PET in conjunction with CT has now been formalized in combination with traditional IWC criteria for assessing response to therapy for NHL. While PET has a high NPV in the pediatric age group, the significance of a positive PET is less clear in this age group. Finally, there are a number of conditions that may mimic lymphoma on PET and CT. An awareness of these, their PET, and CT appearance may help reduce false-positive interpretations of FDG PET/CT.

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