

Anatoliy Granov · Leonid Tiutin
Thomas Schwarz *Editors*

Positron Emission Tomography

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Preface

Recent years have witnessed continuing increases in the incidence of malignant neoplasms, cardiovascular disease, and neurological disorders in most developed countries. At the same time, in spite of significant progress in the development of various medical technologies, there has been substantial growth in cases with an unfavorable outcome (death or disability).

It is well known that the efficient treatment of different diseases depends to a great extent on timely and precise diagnosis, and this is still especially true with regard to the most widespread, severe, and socially significant diseases. Nevertheless, many cancer patients are not diagnosed until they have advanced disease (T3 or T4). Similarly, serious difficulties are often encountered when evaluating the initial symptoms of ischemic heart disease and some neurological disorders. One solution to delayed diagnosis is offered by nuclear medicine in the form of positron emission tomography (PET), which permits precise evaluation of perfusion and metabolism in various organs and tissues and enables opportune identification of the functional disturbances underlying disease development.

PET is an imaging technique that has the distinguishing feature of employing ultra-short-lived (USL) positron-emitting radionuclides for diagnostic purposes. When positrons encounter electrons close to atoms, they both annihilate, producing a pair of gamma photons that travel from the annihilation point in strictly opposite directions and are then registered by detectors situated around the patient. PET with USL radionuclides permits the study of rapid physiological processes (like perfusion and metabolism) at the cellular and molecular level. This ability is fostered by the fact that the widely used positron-emitting radionuclides (carbon-11, nitrogen-13, oxygen-15) are components of numerous biogenic substrata that actively participate in metabolic processes. In principle it is feasible to use a variety of important biological compounds as radiotracers and to synthesize radiopharmaceutical preparations with properties necessary for clinical use.

The foundations of PET were laid in the 1970s by American scientists such as M.M. Ter-Podossian. Development of the method for use in clinical practice was slow and difficult owing primarily to technical problems. The first commercial tomographs appeared only in the late 1970s. They had a restricted number of detectors, they gathered information very slowly, and they had a low resolution.

Distinct visualization of anatomic structures was impossible with these early tomographs. However, in spite of their numerous flaws, the method immediately attracted

close attention from a broad circle of specialists in clinical medicine, including oncologists, cardiologists, neurologists, and surgeons. The very first results of research showed the unique potential of PET to study non-invasively the physiological and biochemical processes taking place in both a healthy and a diseased organism. Initially it was supposed that cardiology would become the main area of application of PET. Today, however, the method is most commonly applied in oncological practice, followed by cardiology and neurology. As the technique was improved and novel radio-pharmaceuticals were developed, new and important data were obtained on the changes in cellular metabolism that accompany transformation of a healthy cell into a cancerous one, on the biological characteristics of tumoral involvement in different kinds of cancer, and on the reactions of tumor cells to treatment. Furthermore, research conducted in the USA, Japan, Western Europe, and Australia showed that the wide introduction of PET into clinical practice would have not only a revolutionary impact on the diagnostic process but also an economic benefit. In particular, it was noted that, in the mentioned countries, investment of \$1 in the development of national nuclear medicine would permit \$1.5–2.5 to be saved in other branches of public health. This is because PET improves diagnosis, permitting disease detection at an earlier stage and timely instigation of appropriate treatment; as a result, it allows the costs of required medicines to be significantly reduced, shortens the duration of in-patient and out-patient treatment, improves prognosis, and reduces disability and mortality in many oncological, cardiovascular, and other diseases.

The above-mentioned advantages of PET, confirmed by the wide clinical experience gathered at the world's leading PET centers, have led to the further rapid development of the technique in recent years. Accordingly, while in 2001 there were 140 PET centers worldwide, performing 255,000 examinations, by 2004 the number of PET centers had risen to 1,500, with 2.5 million examinations. Within the space of 4 years, the number of PET centers in the USA grew sixfold, to exceed 1,000, and the target for 2010 was a further increase to 6,000. Similar rates of development of PET are being observed in most Asian and European countries. In Russia there are currently only six PET centers (three in Moscow and three in Saint Petersburg), some of which function as independent diagnostic surgeries. This time lag in introducing PET in some countries obviously needs to be overcome.

The present handbook provides a systematic account of the physical and technical basis of PET, discusses the organizational principles and methods of examination, and above all examines the clinical use of PET for diagnosis, evaluation of treatment outcome, and detection of disease relapse in various organs and systems. The world's scientific literature has been analyzed and the book also summarizes the authors' 12 years of experience in examining oncological, cardiological, and neurological patients at the PET center of the Russian Research Center for Radiology and Surgical Technologies. The authors hope that their efforts will be of value for specialists starting to master this diagnostic method, for physicians working in one of the branches where PET is applied (oncology, cardiology, neurology, etc.), and for the broad circle of specialists who have recourse to PET in order to solve particular clinical tasks.

Any critical remarks will be accepted with gratitude and taken into account in further editions.

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List of Abbreviations

¹¹ C-MET	¹¹ C-Methionine
¹¹ C-PIB	[¹¹ C]2-(4'-methylaminophenyl)-6-hydroxy-benzothiazol
¹¹ C-PMP	¹¹ N-Methylpiperidine-4-yl propionate
¹¹ C-SB	¹¹ C-Sodium butyrate
¹²³ I-IMT	Tyrosine 1-3- ¹²³ I-methyltyrosine
¹⁸ FDDNP	2-(1-{6-[(2-[¹⁸ F]Fluoroethyl)(methyl)amino]-2-naphthyl} ethylidene)malonitrile
¹⁸ F-FDG	¹⁸ F-Fluoro-desoxyglucose
¹⁸ F-FDOPA	3,4-dihydroxy-6- ¹⁸ F-Fluoro-L-phenylalanine
¹⁸ F-FLT	¹⁸ F-Fluorethyletimidine
¹⁸ F-FLT	¹⁸ F-Fluorothimidine
¹⁸ F-FMISO	¹⁸ F-Fluoromisonidazole
¹⁸ F-FTHA	14(R,S)-[¹⁸ F]-Fluor-6-thia-heptadecan acid
¹⁸ FMPPF	[¹⁸ F]Fluorobenzamido]ethyl]piperazine
3D SSP	3-Dimensional stereotactic surface projection
5HT-receptors	5-Hydroxytryptamine receptors
⁶⁸ Ga-DOTATOC	[⁶⁸ GA]-DOTA-D-Phe1-tyr3-octreotide
AA	Amino acids
AA	Anaplastic astrocytoma
AAD	Aromatic amino acid decarboxylase
ACD	Acute cerebrovascular disease
ACE	Acetylcholinesterase
Acetyl-CoA	Acetyl-coenzyme A
AD	Alzheimer's disease
AFP	σ-Fetoprotein
AIDS	Acquired immunodeficiency syndrome
ARVD	Arrhythmogenic right ventricular dysplasia
ATP	Adenosine triphosphoric acid
AVM	Arteriovenous malformation
BA	Benign astrocytomas
BAT	Bronchioloalveolar tumor
BBB	Blood-brain barrier
BC	Breast cancer
BCC	Bronchioloalveolar cell carcinoma

BDR	Benzodiazepine receptors
BGO	Bismuth germanate oxide
BM	Benign meningiomas
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CC	Compact cyclotron
CEA	Carcinoembryonic antigen
CFA	Coenzyme fatty acid
CG	Continued growth
CG	Chorionic gonadotropin
CHD	Coronary heart disease
CHD	Coronary heart disease
CIT-FP	[¹²³ I]-2 α -Carbomethoxy-3 α -(4-iodophenyl)- <i>N</i> -(3-fluoropropyl) nortopane
CLBBB	Complete left bundle branch block
CM	Cancer metastases
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CPP	Chronic pseudotumoral pancreatitis
CRC	Colorectal cancer
CT	Computed tomography
CT	Computer tomography
CVA	Cerebrovascular accident
CVD	Cerebrovascular disease
DCIS	Intraductal carcinoma in situ
DCMP	Dilatation cardiomyopathy
DCMRI	Dynamic contrast magnetic resonance imaging
DICOM	Digital imaging and communications in medicine
DLB	Dementia with Levy's bodies
DNA	Deoxyribonucleic acid
DOPA	Dihydroxyphenylalanine
DTBZ	(+)- σ -[¹¹ C] Dihydrotetabenazine
DWBS	Diagnostic radioiodine (¹³¹ I) whole-body scans
EC	Esophageal cancer
ECG	Electrocardiography
EEG	Electroencephalography
EF	Epileptic focus
ESR	Erythrocyte sedimentation rate
FA	Fatty acids
FABPpm	Fat acid binding protein of the plasma membrane
FADN	Flavine adenine dinucleotide
FAM	Fibroadenomatosis
FAT	Fatty acid translocase
FATP	Fatty acid transporting protein
FBP	Filtered back-projection

FDG	2-18F-deoxy-D-glucose
FFA	Free fatty acids
FLE	Fiducial localization error
FLE	Frontal lobe epilepsy
fMRI	Functional magnetic resonance imaging
FNH	Focal nodular hyperplasia
FRE	Fiducial registration error
GABA	γ -Aminobutyric acid
GB	Glioblastoma
Gd-DTPA	Gadoliniumdiethylenetriaminepentaacetic acid
GE	General Electric
GIT	Gastrointestinal tract
GLUT	Glucose transporter
GMP	Good manufacturing practice
GMP	Good medical practice
GMR	Glucose metabolism rate
Gr	Grade
GSO	Gadolinium oxyorthosilicate
HBA	Human brain atlas
HC	Huntington's chorea
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HCM	Hypertrophic cardiomyopathy
HCMP	Hypertrophic cardiomyopathy
HD	Hodgkin disease
HD	Huntington's disease
HIV	Human immunodeficiency virus
HMPAO	d,1-Hexamethylpropyleneaminoxime
HNC	Head and neck cancer
HPLC	High performance liquid chromatography
keV	Kiloelectron-volt
LAT	Large amino acid transporter
LC	Lung cancer
LCIS	Lobular carcinoma in situ
LDH	Lactate dehydrogenase
LSO	Lutetium oxyorthosilicate
LVMH	Left-ventricular myocardial hypertrophy
LYSO	Lutetium-yttrium oxyorthosilicate
MALT	Mucosa-associated lymphatic tissue
MAO	Monoamine oxidase
MBF	Myocardial blood flow
MBq	Megabecquerel
MDCT	Multi-detector computed tomography
MFAU	Myocardial fatty acid utilization
MG	X-ray mammography

MGC 20	in Russian – Compact Cyclotron 20
ML	Malignant lymphoma
MLE	Maximum likelihood estimation
MMSE	Mini-Mental State Examination
MnDPDP	Manganese dipyridoxal diphosphate
MRCPG	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MSA	Multisystem atrophy
MSCT	Multislice spiral computed tomography
mSV	Millisievert
MTC	Medullary thyroid cancer
NADN	Nicotinamide adenine dinucleotide
NIEFA	Scientific Research Institute of Electrophysical Apparatus. DV Ephraim
NINCDS	The National Institute of Neurological Disorders and Stroke
OCD	Obsessive–compulsive disorder
OEF	Oxygen excretion fraction
OML	Orbitomeatal line
OMR	Oxygen metabolism rate
OSE	Optimization-space exploration
Palmitoyl-CoA	Palmitoyl-coenzyme A
PAS	Periodic Acid-Schiff
PBT	Primary bone tumors
PC	Prostate cancer
PCHN	Planocellular cancer of the head and neck
PD	Parkinson's disease
PET	Positron emission tomography
PI3K	Phosphatidyl-inositol-3-kinase
PNP	Progressive supranuclear palsy
PSA	Prostata-specific antigen
PTSM	Pyruvaldehyde-bis-4- <i>N</i> -methylthiosemicarbazone
RAMLA	Row action maximum likelihood algorithm
Rb	Rubidium
RCA	Right coronary artery
ROI	Region of interest
RP	Radiopharmaceutical(s)
RSCRST	The Russian Scientific Center of Radiology and Modern Surgery Technologies
RT	Radiotherapy
SAH	Subarachnoid hemorrhage
SC	Stomach cancer
SLM	Solitary lung masses
SLR	Short-lived radionuclides
SOP	Standard operating procedure
SPECT	Single photon emission computed tomography

SPM	Statistical parametric mapping
STT	Soft tissue tumors
SUV	Standard uptake value
SVT	Whole body scintigraphy
T/NT ratio	Tumor to nontumor ratio
T1-WI	T1-weighted image
T2-WI	T2-weighted image
TG	Thyroglobulin
TH	Thyroid cancer
THF	Tetrahydrofuran
TL	Temporal lobe
TLE	Temporal lobe epilepsy
TRE	Target registration error
TRUS	Transrectal ultrasound
TS	Tourette's syndrome
TSH	Thyroid stimulating hormone
US	Ultrasound
USLR	Ultra-short-lived radionuclides
VHL	von Hippel–Lindau tumor suppressor
WBS	Whole-body scintigraphy
WDTC	Well-differentiated thyroid cancer (carcinoma)
WHO	World Health Organization

Part I

Background

1.1 Characteristics of Positron Emission

The method of positron emission tomography (PET) is based on the phenomenon of spontaneous *positron emission* by the nuclei of some unstable ultra-short-lived radionuclides (USLRs), in which the number of protons exceeds that of neutrons. The positron annihilates with an electron, releasing two gamma-photons having the same amount of energy (511 keV) and moving in opposite directions at almost 180° apart (close to collinearly) (Kukekov and Fadeev 1986). Annihilation does not take place in the orbit of its own atom since the positron must first lose its kinetic energy. The length of the flight of the positron from the emission point to the annihilation point depends on its own energy and on the density of the environment. It can fluctuate within a wide range. For example, in the muscle it varies from 1 to 8 mm. This is one of the reasons why PET has a smaller resolving capacity than some other radiodiagnostic methods (MRI, CT). Probably in modern positron emission scanners in which space resolution is 1–6 mm (FWNM), the physical limit of the method's resolving capacity has been reached (Phelps 2004; Gevorksi and Plotkin 2006).

1.2 Principles of Detection of Positron Decay

The main components of a PET scanner are: gantry, movable support (bed) to position a patient in the ring, computer stations to collect and store raw data (the so called sinograms), as well as to reconstruct, process and store images and to obtain hard copies. An important component of the detector ring is the detector block, composed of several crystals connected with a group of photomultipliers in one case. The physical characteristics of the scanner depend to a great extent on the size, form and properties of the materials composing the crystals in the detector block as well as on the diameter of the detector ring.

The interaction between the gamma-photon and the crystal induces scintillation of the latter. As a reaction to scintillation, an electric pulse occurs in the

Fig. 1.1 Scheme of positron decay detection

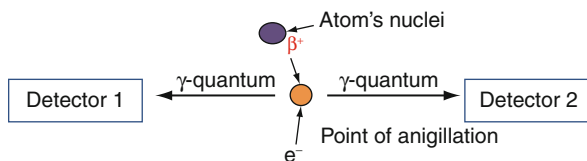
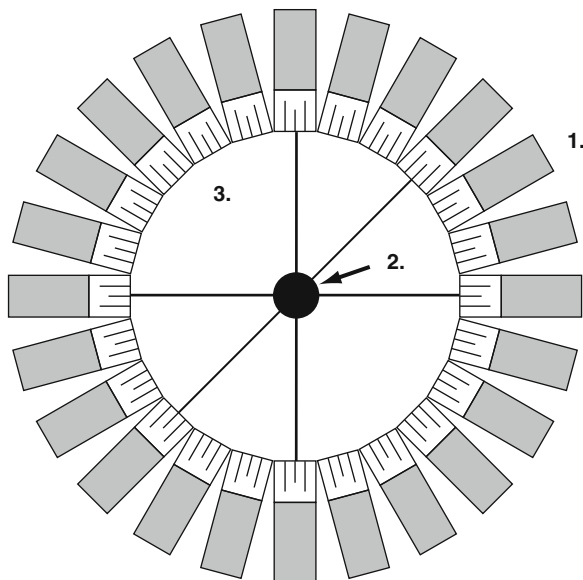


Fig. 1.2 Mechanism of positron (two-photon) emission. Note: 1 the ring of detector-blocks, 2 radiation source, 3 lines going through the radiation source and connecting pairs of detector-blocks



photomultiplier, which can be detected and processed by a computer complex (Gevorski and Plotkin 2006; Khmelev et al. 2004).

In the detector ring of the PET scanner, pairs of highly sensitive detectors, housed in rings, work for coincidence. If a pair of detectors located opposite each other detect two gamma photons within the range of coincidence, we can state that the annihilation point is on the line that unites them (coincidence line) (Fig. 1.1). Annihilation need not necessarily occur exactly in the middle between the detectors. That is why the so called “coincidence window” is used for PET, admitting a temporary deflection of the detection of radiation by pairs of detectors from 4.2 to 12 ns. The event is detected and recorded in the form of polar coordinates (the angle and the radius) in a sinogram. A sinogram is a curve representing the number of recorded events for every coincidence line. The location of every crystal has a space representation in the electronic matrix of the computer which sets the space coordinates of the radiation point. The detection of several lines going through a given annihilation point permits to precisely determine its coordinates (Fig. 1.2). The number of pulses obtained in a given crystal depends on the physical properties of the radioactive

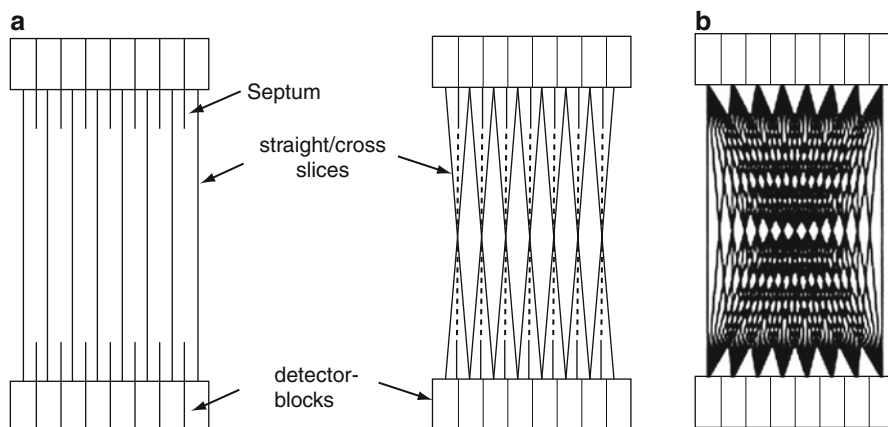


Fig. 1.3 (a) Two-dimensional scanning mode. (b) Three-dimensional scanning mode

source and reflects its qualitative characteristics. The sinogram is processed (reconstructed) by the computer in order to determine the distribution of radioactivity in the slice and to visualize the examined object (Khmelev et al. 2004; Phelps 2004).

Besides genuine coincidences, scattered and random coincidences resulting from different annihilations are detected. Scattered coincidences are related to the Compton effect, according to which they change their movement directions. To separate genuine radiation from scattered and random photons with lower energy, an energy window is used with a center of 511 keV (Khmelev et al. 2004; Phelps 2004; Gevorski and Plotkin 2006).

The above-mentioned characteristics of PET permit a genuine signal to be singled out and detected, satisfying energy and time demands. The indicated way of detecting the signal realized in positron tomographs was called “electronic collimation”. Electronic collimation has replaced the use of physical collimators. Consequently, the sensitivity of PET became higher by a factor of a hundred or thousand compared with single photon emission computer tomography and correct measurements of fast biochemical processes on tomographic slices of any organ or tissue became possible (Khmelev et al. 2004; Gevorski and Plotkin 2006).

To process a signal, some (although not much) time is required during which the detector is not able to detect new events – the so-called “dead time”. The degree of signal loss due to the dead time depends on the speed of the scanner and on the value of radioactivity in the field of view of the tomograph. Contemporary PET scanners are able to maintain a wide range of computing rates without significant losses in resolving capacity (Phelps 2004; Gevorski and Plotkin 2006).

To reduce the number of scattered and random coincidences in PET scanners, limiting screens of lead or tungsten (*septa*) are used. The radiation detection process using a septum is called a two-dimensional (2D) regime; without a septum it is called a three-dimensional (3D) regime (Fig. 1.3). Using a 2D mode permits images with a low-level noise and the highest resolving capacity to be obtained. However, in this

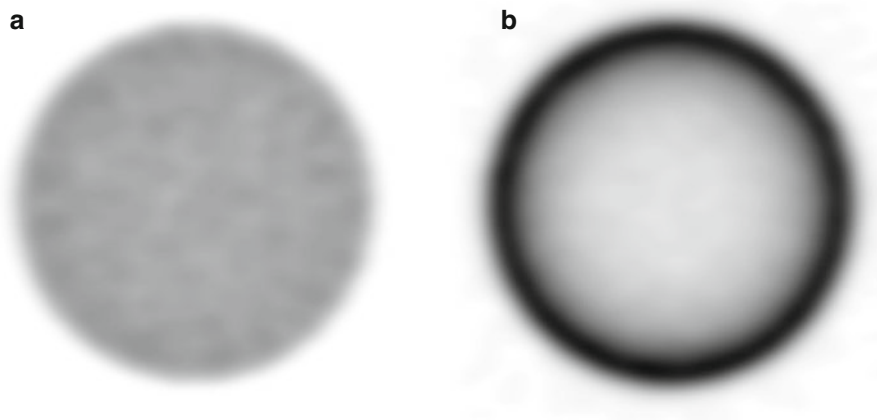


Fig. 1.4 Attenuation correction. (a) Image of the homogeneous ^{68}Ge phantom performed with attenuation correction. (b) The same image performed without attenuation correction

case the sensitivity of the tomograph (i.e., the relation of the number of annihilation acts detected in the field of view of the tomograph with regard to their genuine number in the field of vision) decreases several times; scanner sensitivity being defined by the properties of detector blocks, the diameter of the detector ring, the mode of data acquisition (2D or 3D) and the duration of scanning. The maximum positron scanner sensitivity is achieved by scanning without a septum in the 3D mode (Fig. 1.3b). However, in this case the noise level grows twice and dead time losses increase. The 2D mode, compared with 3D mode, permits a greater accuracy in quantitative analysis and treatment efficiency control to be attained. So, the choice of the scanning mode is conditioned by a particular clinical task. Presently, hybrid PET-CT scanners are produced where there is no septum and only the 3D mode is used.

In PET scanners, photon absorption correction is provided – that is correction for the irregularity of absorption of ionizing radiation by tissues (*attenuation correction*) from radioactive transmission sources of ^{68}Ge and ^{137}Cs (Ruhlmann et al. 1999; Phelps 2004; Gevorksi and Plotkin 2006). This attenuation correction is necessary to compensate for radiation distortion and to attain a higher accuracy of reproducing the distribution of the radionuclide label in tissues. In contemporary tomographs, transmission sources are built into the detector ring. The control is remote, which ensures security and lessens exposure to radiation of the personnel. For example, in Fig. 1.4 we show images of a homogeneous photon of ^{68}Ge with attenuation and without it. The picture shows that the accurate reproduction of radioactive label distribution in a tomographic slice is impossible without absorption irregularity correction. The correction of the irregularity of radiation absorption by tissues is also a necessary component of the quantitative analysis of PET images. In PET-CT combined scanners, digital data are used for this purpose, which are obtained by means of CT. The efficient beam energy of X-rays in CT is 70–80 keV. Consequently, PET images corrected with help of CT attenuation correction differ from images obtained by

using radioactive sources with an energy of 511 keV. For the same reason, PET-CT data processing results in non-linear attenuation coefficients which induce a distortion of the genuine distribution and leads, to overstating radiation accumulation in dense tissues, particularly in the bones. As a result, quantitative measurements of the same formations and tissues done by means of PET and PET-CT scanners can differ by 1.5–2 times (Khmelev et al. 2004; Gevorski and Plotkin 2006). Using contrast agents in CT brings about additional distortions and results in the appearance of artifacts on PET-images, significantly overstating the real radioactivity value in the focus of accumulation of the contrast agent (Gevorski and Plotkin 2006).

In first-generation PET scanners, some part of the equipment was situated outside the tomograph due to its large size and required separate rooms. There were problems concerning speed, screening, and conditioning. The improvement of hardware and video technique and the appearance of personal computers permitted to significantly lessen the size of the main components of PET scanners and to optimize their construction. As a result, the most important parts of modern scanners are located directly in the detector ring. Owing to this circumstance, tomographs became more compact; their speed increased and so did their stability, protection and reliability.

1.3 Reconstruction of Images, Data Processing and Analysis

The initial raw PET data concerning the examined object are collected in the computer in the form of sinograms. The reconstruction procedure permits an image based on sinograms to be obtained. Reconstruction can be performed in several ways. The choice of the particular way of reconstruction depends on the task and on the examined organ. For image reconstructions of such organs as brain or heart, the method of filtered back-projection (FBP or iterative method) is usually used. The iterative method has several modifications, such as MLE, OSE, and RAMLA. In case of whole-body examination, the iterative reconstruction algorithm OSEM is most frequently used, since it ensures the optimal quality of the image owing to smoothing. When brain and heart are examined, it is preferred to use simpler filters which distort least the genuine distribution of radiopharmaceuticals (RPs) in the slices. However, it should be noted that insufficient smoothing, especially when combined with low statistics can increase image heterogeneity, which provides more difficulty in interpreting the results. Too much smoothing can reduce resolution and finally bring about a loss of informativity of the image. Most scanner manufacturers recommend using factory protocols and reconstruction installations, as most are elaborate. A number of reports contain detailed descriptions of the image reconstruction principles and other physical characteristics of the PET method (Khmelev et al. 2004; Phelps 2004; Gevorski and Plotkin 2006).

The course of further image processing (postprocessing) and the obtention of the hard copies of images depend on the particular clinical task. At the first stage, PET-image processing includes their visual analysis in three projections (axial, sagittal and coronal projections). In the case of the whole-body examination, 3D image analysis

is applied, which provides a more accurate idea of the localization and anatomical links of the examined area. The image standardization procedure is described separately for each organ in the corresponding chapters of the present book.

A necessary condition of a successful analysis is the precise knowledge of the normal distribution and pharmacokinetics of the RPs which are used. The notion of the physiologic (normal) distribution is specific for each RP and depends on its properties. Therefore the presentation of the results obtained comprises both the visualization of the state of the unaffected organs examined or of the whole body and the characteristics of the lesion area, including its localization, scintigraphic size, and regularity of RP distribution, contour accuracy and its relation to unaffected tissues. These tasks are solved as a rule by using image contrast range, colour scales and threshold level. The absence of anatomic reference points in the functional images provides certain problems concerning the interpretation of scintigraphic images. This is why in a number of cases accurate matching or fusion of images with different modalities is needed. Matching of functional PET images and the data of structural imaging (CT, MRI) is first of all required for an accurate anatomic localization of the revealed changes; it is also needed in the presence of significant physiological (individual) fluctuations of the levels of RP uptake in tissues. Besides, superimposing is necessary when the formation's size is small and close to the resolving capacity of the tomograph and also when the formation has a high structural heterogeneity.

At the second stage, quantitative or semiquantitative PET-image analysis in absolute and relative values are applied. For semiquantitative analysis of the objects examined in whole-body examination, and since recently also in brain examination, a dimensionless value is used – the so-called standardized uptake value (SUV). SUV is defined as the relation of specific radioactivity in the measured zone (kBq/cm^3) to the value of the introduced radioactivity per body mass MBq/kg . SUV is automatically calculated by the software of the scanner, taking into account the physical half-life period of the radionuclide. In image analysis using SUV, it should be noted that imprecise information on the patient's weight and stature, the value of the introduced radioactivity and the time of its introduction as well as on the detector drift can induce serious errors. This is why it is accepted to consider as significant an SUV change during treatment which is more than 25% of the initial value.

Tumor/nontumor (T/NT) ratio is used to express the relation of radioactivity accumulated in the affected area to radioactivity in unaffected tissues (referent zones). In some cases it is appropriate to apply mathematical models implying dynamic scanning of the examined organ to calculate the “input function” – a curve of activity-time in arterial blood. To measure blood radioactivity, it is most convenient to scan the left ventricular cavity. Mathematical models are widely used in heart examinations: on the one hand, the high variability of metabolic processes in this organ limits the possibility of using simple quantitative analysis methods; on the other hand, the presence of the left ventricular cavity in the field of view of the tomograph makes it simpler to obtain the inline function.

1.4 Pet Data Quality Control

PET data quality control methods are divided into acceptance trials, regular control and parameter change of the tomograph during its exploitation. Acceptance trials are done during the installation of the equipment. In the process of trials, initial data on the operation factors of the scanner are obtained, which then serve as a model in daily or recurrent technical state control. Modern scanners are provided with reliable and easy-to-use means of control and image quality correction as well as of quantitative data reproducibility: normalization, cross-calibration and other procedures. During daily control, the deviation of the readings of detectors from the mean is automatically calculated, which permits evaluation of their state, revealing deviations from the admissible parameters and identifying and localizing faults. Normalization is carried out if the admissible deviation of the sensitivity of the opposite pairs of detectors is exceeded by more than 2.5%. For this purpose, a standard calibration phantom with determined specific radioactivity is brought into the field of view of the scanner. During normalization, the so-called “blank scan” is created which is necessary to align as much as possible the field of view of the scanner during image reconstruction. During normalization, the calibration factor (ECF) is also calculated, which is an integrated factor reflecting detector drift, physical decay of calibration sources and some other parameters having impact on the precision of the measurement. The value of ECF is specific for a given model of tomograph and depends on its construction. This factor is used also as a criterion of quantitative data reproducibility. For example, an ECF value deviation of more than 5% from its previous value requires aligning the field of vision of each of the detector blocks (set up). Homogenous calibration phantoms are fabricated using positron-emitting radionuclides (^{68}Ge , ^{137}Cs) with a half-life of 1–10 years. Radionuclides should be evenly distributed in the phantom. Measurement of a radionuclide is possible only before its introduction into the phantom and is carried out by means of a curiemeter. RPs are injected to the patient in the form of aqueous solutions; their radioactivity measurement is done in a given PET center. For matching of factory ^{68}Ge phantom and a water phantom of known specific activity prepared in the PET center when changing calibration sources recalibration is performed. The accuracy of recalibrating the sources has an impact on the calibration factor (ECF) and on the outcome of the quantitative analysis in a given scanner (Khmelev et al. 2004; Phelps 2004; Townsend et al. 2004; Gevorski and Plotkin 2006).

Consequently, the available hardware arsenal ensures reliable PET data image and reproducibility quality control, which is crucial for clinical application of the method.

There can be hardware, software, control, biological and mixed *artifacts*. As a rule, hardware malfunctions are revealed during the daily checkup, which enables details of the damage to be determined. Sinogram analysis is also used for this purpose. The most frequent cause of hardware malfunctions is due to analog processors or bucket controllers getting out of order. When an analog processor gets out of

order a stripe appears on the sinogram which corresponds exactly to the damaged processor. If a controller is damaged, the stripe is wider and it embraces all the processors of the controller. Damage to the detector block is revealed during daily calibration. The damaged block is identified by scanning according to a special program or by a “set-up” procedure. Identifying program or mixed errors is a more difficult problem. For example, the procedure of pulling out radioactive calibration sources from containers is carried out by applying a special programme. An error in its working makes the radioactive sources stop. This can look like a breakdown of the mechanism making them move out.

The operator’s errors (entering wrong information on the patient or on the introduced radioactivity) can be corrected by introducing the necessary amendments into the sinogram header with its subsequent repeated reconstruction. At the same time, errors in the data collection protocol or in positioning patients cannot be corrected retrospectively.

The causes of artifacts may also be due to injection errors, whereby some part or all of the RP is left in the injection spot, the radioactive substance flowing out from the vein together with blood and onto a soiled dressing; they may also be due to contamination with radioactive urine. When a radioactive substance gets to the patient’s arms and clothes it can be also transferred to the scanner; for example, to the patient bed of the tomograph. In this situation, one or several superficially located uptake foci appear on the image which can induce false-positive diagnostics of some diseases, for example in melanoma. Contamination detection always provides some difficulty. This is why an important way of dealing with artifacts is observing the methodology and having an accurate idea on the possibility and place of their appearance. In case of a suspicion of a contamination artifact, one can try to wash the radioactive substance off the skin surface, take off the contaminated clothes, change linen on the tomograph and wipe its surface. Another cause of artifacts is the patient’s displacement during scanning or moving organs (e.g., heart or lung excursion), which bring about a fuzzy image.

1.5 Modern Positron Emission Scanners and Hybrid PET/CT Scanners

Intensive work on developing and modifying PET scanners carried out in the 1980s resulted by the early 1990s in creating the generally accepted multiring scheme using highly sensitive detectors on the basis of crystals of bismuth germinate oxide (BGO). For example, in 1984 large-scale production of PET scanners of the ECAT series was started in the USA (CTI) and Germany (Siemens), which were widely used in the world in several modifications. At present, the main positron emission scanner manufacturers are Siemens, GE, (USA) and Philips (The Netherlands). The successive development of PET technology resulted in creating in 2000 a micro-PET system and then a micro-PET-CT system which have a high resolution (~ 1 mm) and are needed for laboratory research.

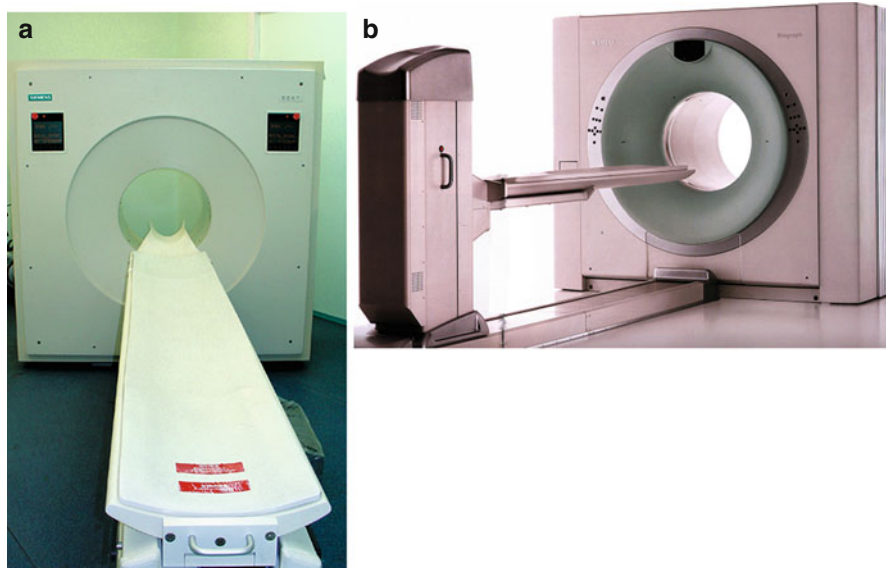


Fig. 1.5 PET and PET/CT scanners by Siemens (Germany). (a) Ecat Exact HR+ PET scanner. (b) Biograph PET/CT scanner

Since 2001, lutetium oxyorthosilicate crystals (LSO) and lutetium-yttrium oxyorthosilicate crystals (LYSO) have started to be applied in the detector blocks of positron scanners; these materials being even more sensitive to gamma rays than BGO. Positron tomographs with detector blocks using such crystals have obvious advantages over their precursors. Given these improvements, mass production of combined PET/CT scanners began in 2002; these apparatuses permit different modality images to be superimposed with high precision.

These PET scanners can be divided into five groups. The first group (PC 2048-15B, Ecat Exact 31) comprises scanners having a narrow field of view, which does not permit single-stage examination of the heart or brain to be carried out. These scanners had a relatively low sensitivity and resolution. This is why they have been taken out of production and are not used anymore. The scanners Ecat ART, C-PET+ and Ecat Exact 47 enable single-stage examination of organs such as brain or heart. Scanners of this group are also used for whole-body examination. Their difference from the third group (Ecat Exact HR+, Advance) is in lower sensitivity and resolution. The second and third groups of PET scanners satisfy the demands put upon apparatuses for clinical use and are still widely used in clinical medicine (Fig. 1.5a).

Scanners of the fourth group (Ecat Accel) successfully combine the simplicity and reliability of construction typical of the second group and relatively high sensitivity and resolution due to using LSO crystals. Finally, the fifth group consists of combined PET/CT scanners (Fig. 1.5b), having new performance capabilities

compared with separate scanners. In modern PET/CT scanners, LSO or LYSO crystals with a minimum size are used; they also include many detector rings. This permits the combination of high resolution and a field of view sufficient for single-stage scanning of the brain or heart. However, in spite of obvious progress, presently production of PET scanners is stopped. The advantages of combined PET/CT scanners are obvious. They include, among other things, the possibility of precisely superimposing different modality images, short scanning time due to using CT data for attenuation correction, high sensitivity and resolution, and, as a result, high image quality. Simultaneous acquisition of functional and anatomic images can significantly improve the quality of patient examinations due to more accurate the spatial localization of RF uptake foci currently, all manufacturers of diagnostic equipment produce only combined PET/CT scanners. PET/CT system allows to obtain the functional (PET) and structural information (CT) by PET and CT images coregistration for a single study. In addition, CT data can be used for attenuation correction. The Application of CT based attenuation correction reduces the time of the examination by 30–40%. Structurally, the PET/CT system is a PET and CT scanners are placed in a single gantry. Usually CT scanner is located in front of PET system. Modern PET/CT scanners have a gantry aperture of 70 cm and a width of 100 cm. The first stage of data acquisition is obtaining a scout topogramm to localize the scan area. CT scan is performed at a voltage of 100–140 kV and different power supply (depending on the purpose of the study). After that a patient is automatically moved to the PET scanner in the same anatomical position. PET study takes 3–5 minutes. Then the PET images are reconstructed using CT –based attenuation correction. PET image matrix size is 128×128 and CT is 512×512 . The limitations of the combined PET/CT scanners compared with PET tomographs are due to CT artifacts in case of metal objects appearing in the field of view of the scanner (e.g., crowns, dentures, etc.) The problem of breathing motion is still not completely solved, when CT is carried out with breath-holding at suspended inspiration and PET is performed without it. As pointed out above, using CT for attenuation correction of emission images may induce distribution distortion, heightening radioactivity accumulation in dense tissues, particularly in bones. Finally, a more complex construction is related to a higher price and lesser reliability, whereby the results of the examination are less certain.

Ensuring reliability of the work of a PET center is crucial. One way to solve this complex and many-sided problem consists of immediately changing faulty equipment, which is ensured by duplicating it. Duplicating also improves the capacity of the PET center and is widely used all over the world. In its turn, capacity, besides scanner rapidity, depends on reducing technological process duration, quickly making the tomograph ready for subsequent examination, quick reconstruction and image processing, preparing hard copies, data archiving, etc. The scanner should provide for a possibility to work in the static and dynamic modes with several RPs, labeled by different radionuclides. Successful use of the positron scanner in a particular clinical situation also depends on the diameter of patient port, which should

make it possible to examine corpulent patients, on the solidity of construction of the tomograph, on the possibility to break scanning at any stage if need be and to recommence it, etc.

Modern clinical positron emission scanners are intended for examining any organ or the whole body and the internal diameter of their ring (patient port) is up to 600 mm. The patient bed can support up to 160 kg of body weight. The width (axial dimension) of the field of view (15–25 cm) enables single-stage examinations of organs such as brain or heart to be performed. Positron scanners of the last generation are characterized by high resolving capacity, high sensitivity, efficient algorithm of image reconstruction, processing, presenting and archiving (Valk et al. 2003; Khmelev et al. 2004; Phelps 2004; Townsend et al. 2004; Gevorsi and Plotkin 2006).

1.6 Production and Properties of Ultra-Short-Lived Radionuclides for PET

1.6.1 Cyclotron Production of Positron Emitters

In order to obtain ultra-short-lived positron-emitting radionuclides, special highly technological equipment is necessary; its main components are a cyclotron complex and a radiochemical laboratory with an RP quality control department (European Pharmacopoeia 1996; Valk 2003; Phelps 2004; Baranov 2005).

A *cyclotron* (elementary particle accelerator) provides the production of radionuclides for medical use. Heavy particles, mainly protons and deuterons, are accelerated to an energy level of 5–100 MeV or more. A target substance is bombarded with heavy particles to produce the required radionuclides. Cyclotron constructions may vary significantly, depending on the materials used, maximal energy of the accelerated particles and radiation safety. Modern compact Russian cyclotrons and those from elsewhere, besides their small size, have automatic remote control and are able to irradiate simultaneously two and more target devices. Modern cyclotrons are as a rule provided with biological protection, which makes them simpler in service and simplifies room size and design requirements.

Elementary particles accelerated in the cyclotron reach special targets filled with the target substance. Nuclear-chemical reactions occur in the irradiated target substance, whereby radionuclides of the required chemical form are obtained (Tables 1.1 and 1.2). The beam of particles is focused on the target substance by a special controlled radio-magnetic “lens”. The construction of targets should provide airtightness, reliable cooling and process control; their form, size and material also permit to bring the beam of particles to the target substance without significant losses. During irradiation it is necessary to control the current on the target, pressure and temperature, etc. The current should correspond strictly to the produced radioactivity. If the current on the target is lower than estimated, it will cause a significant

Table 1.1 Main nuclear-physical properties and obtention reactions of some cyclotron-produced USL-radionuclides

Description of the radionuclide	$T_{1/2}$	Energy of gamma-quanta (keV)	Linear positron track until annihilation (mm)		Target substance ^a	Type of reaction ^a	Energy of positrons (MeV)	Portion of positron decay
			Maximum	Middle				
Oxygen-15 [¹⁵ O]	2.03 min	511	8.2	1.5	¹⁴ N ₂ + O ₂	¹⁴ N(d,n) ¹⁵ O	1.72	100% β+
Nitrogen-13 [¹³ N]	9.96 min	511	5.4	1.4	H ₂ ¹⁶ O	¹⁶ O(p,α) ¹³ N	1.19	100% β+
Carbon-11 [¹¹ C]	20.4 min	511	5.0	0.3	¹⁴ N ₂	¹⁴ N(p,α) ¹¹ C	0.96	100% β+
Fluorine-18 [¹⁸ F]	109.7 min	511	2.4	0.2	H ₂ ¹⁸ O	¹⁸ O(p,n) ¹⁸ F	0.64	97% β+, 3% e-capture
Bromine-76 [⁷⁶ Br]	16.2 h	511	–	–	⁷⁶ Se	⁷⁶ Se(p,n) ⁷⁶ Br	3.4	57% β+
Iodine-124 [¹²⁴ I]	99.6 h	511	–	–	¹²⁴ Te	¹²⁴ Te(p,n) ¹²⁴ I	2.1	23% β+, 77% e-capture

^aOne of the variants of using obtention reactions and target substances is adduced

Table 1.2 Principal nuclear-physical properties and obtention reactions of some generator-produced USL radionuclides

Description of the radionuclide	$T_{1/2}$ (min)	Energy of gamma-quanta (keV)	Mother radionuclide	$T_{1/2}$ (24 h)	Positron energy (MeV)	Portion of positron decay
Rubidium-82 [⁸² Rb]	1.25	511	[⁸² Sr]	25.5	3.35	95% β+, 5% E-capture
Gallium-68 [⁶⁸ Ga]	68.1	511	[⁶⁸ Ge]	271	1.90	90% β+, 10% E-capture

decrease in output; if it is higher, it will provoke overheating and subsequent loss of pressure and damage to the device. The duration of irradiating the target substance usually corresponds to the half-life period of the obtained radionuclide. For example, the time of irradiating heavy water to supply a 70% yield of fluorine-18 possible for a given target is 2 h. This corresponds to the physical half-life of fluorine-18. One more hour of irradiating adds only 10% radioactivity, which is due to the simultaneous decay of the radionuclide.

Cyclotron-produced positron-emitting USLRs (the so-called bioelements) include oxygen, nitrogen and carbon isotopes (¹⁵O, ¹³N and ¹¹C). These radionuclides may be built into different substances by substituting a radioactive atom for a non-radioactive one. Metabolic properties of substances do not change after this substitution. This set of radionuclides enables almost any biologically active molecules to be labeled. Besides bioelements, other cyclotron-produced radionuclides are used, for example fluorine and iodine isotopes (¹⁸F and ¹²⁴I), as well as

generator-produced USLRs such as isotopes of rubidium (^{82}Rb), gallium (^{68}Ga) and others. All positron-emitting USLRs have the same measurable energy of gamma-quanta, 511 keV, which precludes simultaneous use of two radiopharmaceutical preparations in one patient. When using USLR labelers, contrary to usual short-lived radionuclides, it becomes possible to examine fast processes (metabolism, perfusion) at the cellular and molecular levels, radiation load to the patient is reduced and combined or repeated examinations can be performed within short delay without exceeding the acceptable radiation load limits. A $^{68}\text{Ge}/^{68}\text{Ga}$ generator (the half-life of gallium-68 is 68 min) is successfully applied for labeling peptides.

We should also mention the $^{82}\text{Sr}/^{82}\text{Rb}$ generator, which permits $^{82}\text{RbCl}$ with a physical half-life of 75 s to be obtained.

$^{82}\text{RbCl}$ is used in clinical cardiology to measure regional myocardial perfusion. A more detailed description of the nuclear-physical properties and reactions for obtaining radionuclides can be found in the following works: (Nemets and Hoffman 1975; European Pharmacopoeia 1996; Dmitriev et al. 2001; Korsakov 2002; Baranov 2005).

Radiopharmaceuticals are produced in the *radiochemical laboratory*. Short half-lives of USLR require high level radioactivity to be supplied. This is why a radiochemical laboratory should be equipped in a sequence of special protective (“hot”) cells (Fig. 1.6a, b).

As can be seen in the picture, boxes can have different types of construction and protection depending on the desired value of RP radioactivity. In the boxes automated modules are located which permit to synthesize RP as quickly as needed (Fig. 1.6c–e).

In case of an unexpected situation caused by the breakdown of a module or by an error on the part of the personnel, one has to wait for radiation in the module to decrease to acceptable levels and to remove the malfunction. Hence the best solution that ensures uninterrupted work of the laboratory is equipment duplication, especially in case of RP synthesis modules based on fluorine-18.

Using automated injection systems is crucial. Automated injection systems are the only accurate and secure way of dosing and injecting for RPs based on the most short-lived radionuclides such as ^{82}Rb or ^{15}O . In the absence of a cyclotron and radiochemical laboratory, fluorine-18-labeled RPs or those labeled by other USLRs and SLRs with half-life of 2 h or more may be transported to other medical institutions no longer than during one half-life period of the radionuclide. That is why all oxygen-15-, nitrogen-13- and carbon-11-labeled RPs cannot be transported and can be used only in the institution in which they are produced. For this reason, developing and applying generator radionuclides or RPs for PET is of great interest.

The modern radiochemical laboratory has to correspond to GMP requirements. These requirements constitute a set of rules for producing medicinal and diagnostic agents concerning all aspects of the production technology as well as of quality control, and is intended to guarantee their quality, reliability of synthesis and security of use.

Fig. 1.6 Russian RP production complex satisfying GMP demands. (a) Chain of protective (hot) boxes provided with robots for RP synthesis; (b) separate protective box. Complex of automated modules for the synthesis of ^{18}F -FDG (c), ^{11}C -sodium butyrate (d), ^{13}N -ammonium (e), and methods of quality control of a ready production codeveloped by the Institute for Theoretical and Experimental Physics (Moscow), Politechnical University and RRCRST of the Ministry of Health of the RF, Saint Petersburg

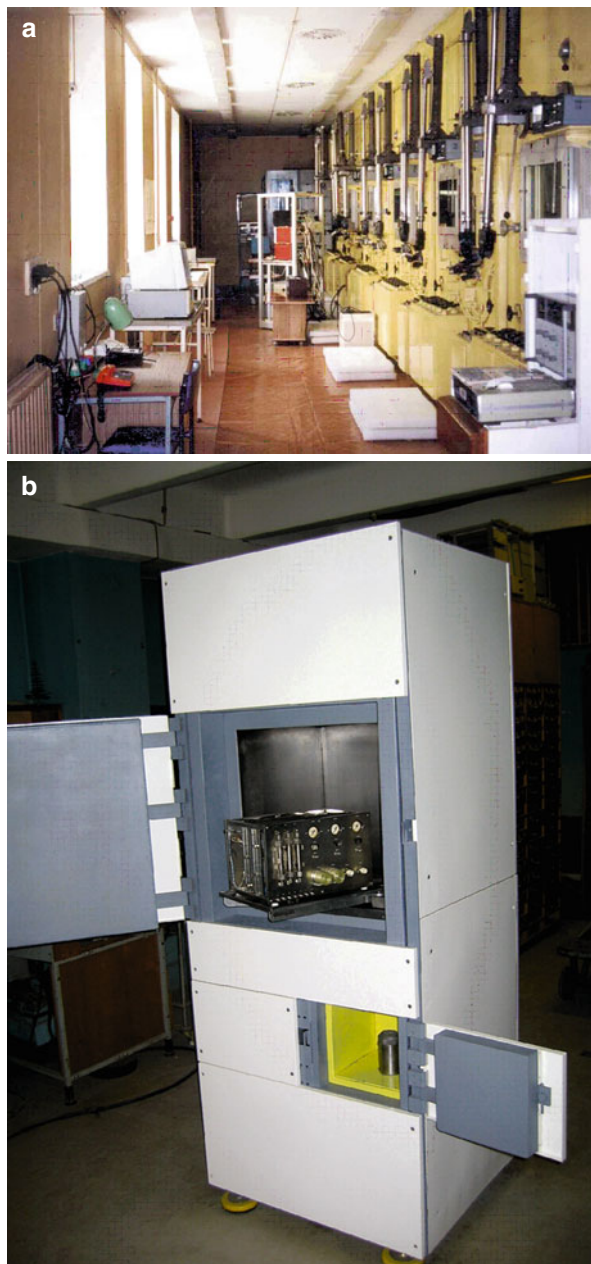


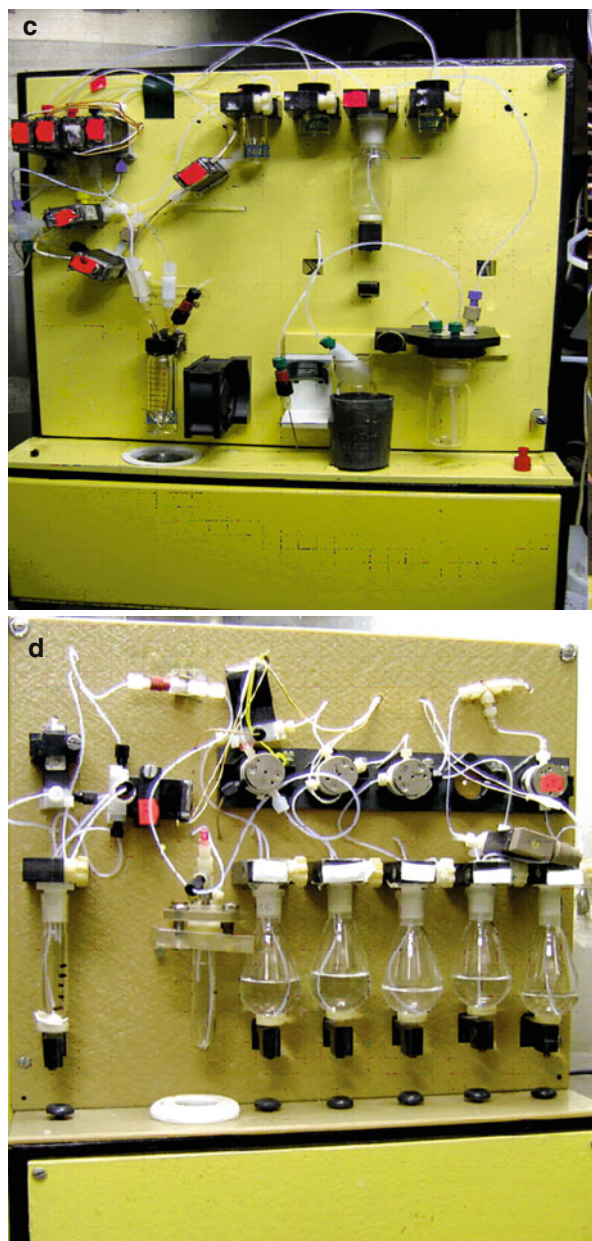
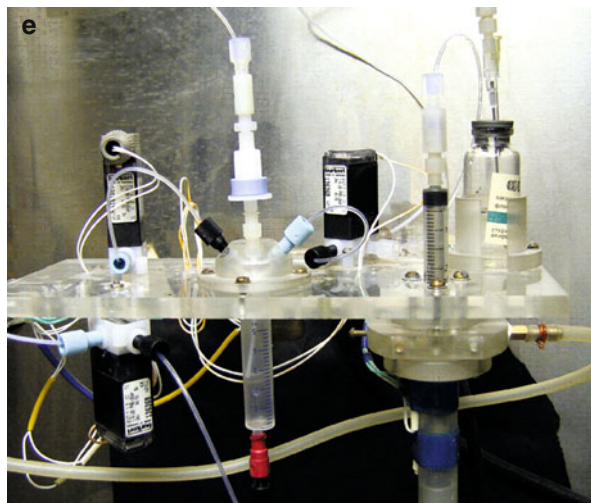
Fig. 1.6 (continued)

Fig. 1.6 (continued)

In the *quality control department*, quality control of ready-to-use radiopharmaceuticals is carried out. Quality control includes determining radiochemical purity of the RP by means of high-performance liquid chromatography, determining residual solvents by gas chromatography, pH measurement and saline composition measurement. Radionuclide purity control is carried out by a gamma-spectrometer, sterility is tested by inoculations, and pyrogenicity (presence of bacterial endotoxins) is tested by special methods. The measurement of pH, high-performance liquid chromatography and gas chromatography are carried out before injecting the RP into the patient or during the first (control) synthesis of a given series of RPs if USLRs are used. After the radioactivity value is measured in the dose calibrator, a registration certificate and permission to inject a given RP are issued. Other measurements (spectrometry, sterility and pyrogenicity determination) are performed after using most RPs based on USLRs, with the exception of fluorine-18 labeled RP, for which spectrometry is possible before injecting.

The RP packing is accompanied by the registration certificate where the series number, RP description, volume radioactivity, general radioactivity during measurement in the radiochemical laboratory, volume, radiochemical purity, pH value, expiration date and packing type are indicated. The registration certificate is an obligatory document confirming the possibility of diagnostic use of a given RP series.

There are two ways of determining RP dosage: by the volume and radioactivity indicated in the registration certificate (according to the results of the measurement performed in the radiochemical laboratory) or by means of direct measurement with a dose calibrator in the PET department. Dosing RP by volume, considering the decay of the radionuclide, is carried out according to a formula or nomograms. This simple way of dosing permits to save time but can induce errors in calculating

the injected RP dose, the errors increasing with time. Direct measurement of the injected RP dose enables calculation errors to be avoided. However both approaches are possible in a real clinical situation.

1.7 Methods of Obtention and Properties of Some RPs Used for PET

Diagnostic capacities of the PET method are determined not only by the physical and technical capacities of the scanner, but also by the properties of RPs used for examinations. Usually in radionuclide diagnostics several tens of RPs are used, whereas the total number of RPs synthesized for PET amounts to several hundreds and is permanently increasing. Growing technical and scientific interest in RPs for PET is due to the fact that any biologically active substances can be labeled by USL radionuclides without changing their properties. For example, labeled amino acids, glucose, fatty acids, gas, and water are used for PET. The possibility of labeling with different USLRs has developed for some of the most important substances; for example, for amino acids and glucose. Using labeled substances enables their properties to be studied *in vivo*. Besides their direct clinical use for the diagnostics of diseases, these data are crucial for solving some scientific problems.

The choice of a radionuclide for labeling is conditioned not only by the composition of the substance and by the necessity of using simple, reliable and secure RP synthesis methods, but also by requirements of the physical half-life of the radionuclide label. In particular, in order to evaluate the pharmacodynamics of substances whose effective half-life makes several tens of minutes or hours, one cannot use USLRs with physical half-lives measured in seconds or minutes. Although fluorine-18 is not a bio-element, most promising and widely used RPs are created on its base.

In Table 1.3 the main RPs most widely used in clinical practice are listed. The advantages of these RPs became obvious after many years of theoretical and practical studies of their properties and diagnostic capacities. For example, the RP ^{11}C -glucose accurately reiterates all the stages of glucose metabolism and its use appears at first glance as more promising than ^{18}F -FDG, which in fact reflects only glucose transport across cell membranes. However, when ^{11}C -glucose is injected the radioactive label is excreted in the form of $^{11}\text{CO}_2$ equally rapidly from tumorous and non-tumorous cells, which does not permit to distinguish them. This is why practical use of this RP in oncology provides difficulty.

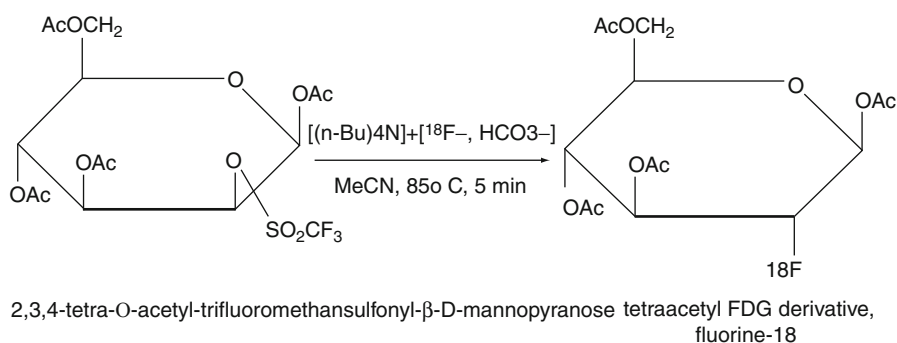
^{18}F -fluoro-desoxyglucose (^{18}F -FDG). Two main approaches to ^{18}F -FDG synthesis are described. The first one is based on the electrophilic triacetylglucal fluorination reaction. The second one is based on the reactions of nucleophilic substitution of a triflate group by ^{18}F generated in the target when oxygen-18 nuclei are irradiated by a beam of protons with energy of 15–17 MeV according to the reaction $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$. Presently the nucleophilic method is widely used as it is more efficient and stable.

Table 1.3 Radiopharmaceuticals for PET widely used in clinical practice

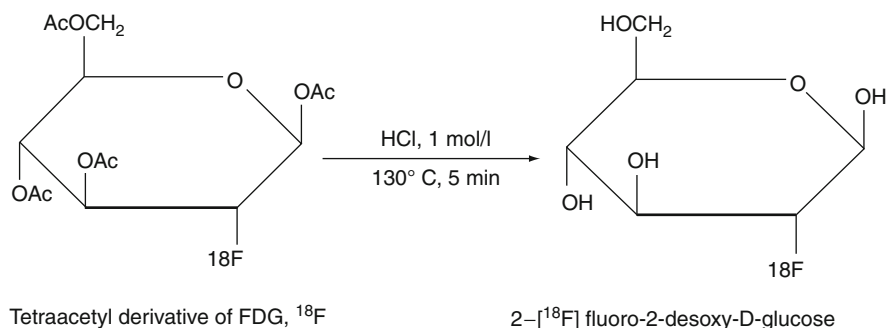
N	Radio-nuclide	Substance	RP description	Purpose of the indicator and its range of application
1.	[¹⁵ O]	Water	¹⁵ O-water	Speed of regional blood flow (in brain)
2.	[⁸² Rb]	Rubidium chloride	⁸² Rb chloride	Speed of regional perfusion (in myocardium)
3.	[¹³ N]	Ammonium	¹³ N-ammonium	Speed of regional perfusion (in myocardium)
4.	[¹¹ C]	Methionine	¹¹ C-methionine (¹¹ C-MET)	Speed of protein synthesis (in brain tumors)
5.	[¹¹ C]	Tyrosine	¹¹ C-tyrosine	Speed of protein synthesis (in brain tumors)
6.	[¹¹ C]	Thymidine	¹¹ C-thymidine	Speed of proliferative activity in tumor cells
7.	[¹¹ C]	Choline	¹¹ C-choline	Speed of phospholipid synthesis – marker of membrane-forming (prostate cancer and its metastases)
8.	[¹¹ C]	Acetate	¹¹ C-acetate	Speed of oxidative metabolism (in myocardium and brain)
9.	[¹¹ C]	Palmitic acid	¹¹ C-palmitic acid	Speed of fatty acid metabolism (in myocardium)
10.	[¹⁸ F]	Fluorine desoxyglucose	2-[¹⁸ F]-fluorine-2-desoxy-D-glucose (¹⁸ F-FDG)	Speed of the metabolism of (transmembrane transfer) of glucose
11.	[¹⁸ F]	DOPA	¹⁸ F-fluorine-dihydroxyphenylalanine (¹⁸ F-DOPA)	Concentration of dopamine receptors in brain and in some tumors (medullary thyroid cancer, pancreas tumors, GIST, brain tumors)
12.	[¹⁸ F]	Thyrosine	¹⁸ F-fluoro-ethyl-tyrosine (¹⁸ F-FET)	Speed of transmembrane transfer of amino acids (in tumors)
13.	[¹⁸ F]	Fluoride	¹⁸ F-ion (fluoride)	Speed of calcium metabolism (revealing bone metastases)
14.	[¹⁸ F]	Thymidine	3-deoxy-3-[¹⁸ F]-fluorothymidine (¹⁸ F-FLT)	Speed of proliferative activity in tumor cells
15.	[¹⁸ F]	Choline	¹⁸ F-choline	Speed of phospholipid synthesis – membrane-forming (prostate cancer and its brain metastases, oesophagus tumors)

The main RPs for PET are marked in bold

The radiochemical synthesis of 2- ^{18}F -fluoro-2-desoxy-D-glucose (^{18}F -FDG) can be carried out by means of an automated module, for example, Nuclear Interface (Germany). The volume activity of the RP may reach 2.0 GBq/mL. The duration of synthesis when a module is used it is 25–30 min. In most cases, ^{18}F -FDG synthesis is performed according to the two-stage method of Hamacher. The first stage of the synthesis includes the reaction of nucleophilic substitution of the triflate group of 1,2,3,4-tetra-*o*-acetyl-trifluoromethansulfonyl- β -D-mannopyranose by fluoride-18 with participation of interphase catalysts according to the reaction:



The second stage comprises removing the acetyl protection by acid hydrolysis of the intermediate tetraacetyl derivative of ^{18}F -FDG under the influence of hydrochloric acid at a high temperature.



Purification of the RP is performed by passing it through microcolumns filled with adsorbents – reverse-phase ion exchange resins. Then the RP is sterilized by passing through a Millipore filter with pores of the size 0.22 μm .

The final RP is a colorless transparent isotonic sterile and non-pyrogenic solution containing fluorine-18 in the form of 2- ^{18}F -fluoro-2-desoxy-D-glucose (Korsakov et al. 1992; Korsakov 2002; European Pharmacopoeia 1996).

Characteristics of the RP:

Form	Transparent colorless liquid,
Radionuclide purity	No less than 99%,
Radiochemical purity	No less than 95%,
pH	5.0–7.0.
Composition:	
Sodium chloride	8.5–10.0 mg,
Water for injection	Up to 1.0 mL,
[¹⁸ F]	40–2,500 MBq.

¹¹C-methionine (¹¹C-MET). Carbon-11 is obtained by irradiating nitrogen-14 nuclei with a beam of accelerated protons according to the nuclear reaction ¹⁴N (p,α)¹¹C. The chemical form of stabilization of carbon-11 atoms is carbon dioxide generated by the interaction of carbon-11 with oxygen present in the target gas as an admixture.

The most widely used amino acid in PET is carbon-11-labeled methionine (¹¹C-methionine). ¹¹C-methionine is an isotonic sodium dihydrophosphate solution containing the radionuclide carbon-11 in the chemical form of “L-methionine, ¹¹C” in the position of methyl group without adding a carrier. The irradiated carbon dioxide is transported from the target to the synthesis module, where it is passed through a lithium aluminiumhydride solution in the THF. Then the THF is evaporated and 57% hydroiodic acid is added. The generated methyl iodide is distilled off at a high temperature. To synthesize the RP L-methionine, ¹¹C, the reaction of methylation of L-homocysteine thiolactone by carbon-11-labeled methyl iodide is used. For this purpose, the generated “methyl iodide, ¹¹C” is passed through a column prewetted with a water-alcohol solution of L-homocysteine thiolactone. The obtained “L-methionine, ¹¹C” is washed with a sodium dihydrophosphate solution through the purifying cartridge and sterilizing filter (European Pharmacopoeia 1996; Korsakov 2002).

The total synthesis duration amounts to 15–29 min; the volume activity at the end of synthesis is 0.2–1.0 GBq/mL.

¹¹C-methionine has the following characteristics:

Form	Transparent colorless liquid;
Radiochemical purity	>95.0%,
Radionuclide purity	>99.5%,
pH	6.0–8.0.
Composition:	
Sodium dihydrophosphate	9 mg,
Injection water	Up to 1.0 mL
[¹¹ C]	0.2–1.0 GBq.

¹³N-ammonium. Nitrogen-13 radionuclide is obtained by irradiating oxygen of natural isotopic composition according to the reaction ¹⁶O(p,α)¹³N. Water is used as a target substance; it is irradiated by a beam of protons with energy 15 MeV. To

produce the “ammonium, nitrogen-13” RP, a nuclear chemical method is used which permits the RP to be obtained directly in the cyclotron target. When irradiating water of natural isotopic composition under pressure of hydrogen, the chemical form of stabilization of nitrogen-13 is the $[^{13}\text{N}]$, NH_4^+ cation.

After the purifying column, water passes to the intermediate vessel of the installation, which contains a sodium chloride solution, where the half-product that is $[^{13}\text{N}]$, NH_4Cl solution is obtained (European Pharmacopoeia 1996; Korsakov 2002).

The characteristics of the RP:

Form	Transparent colorless liquid
Radionuclide fluorine-18 admixture:	No more than 0.5% for the production time,
Radiochemical purity:	No less than 95.0%.
Composition:	
Sodium chloride:	9.0 mg,
Deionizer water:	1.0,
$[^{13}\text{N}]$	0.2–2.0 GBq.

1.8 Diagnostic Properties of PET RPs Used in Oncology

^{18}F -FDG is a non-specific tumor-seeking RP and it is widely used for the diagnostics of malignant tumors. The applicability of a given RP in oncology is based on the phenomenon of heightened glycolysis in neoplasms, described by Otto Warburg in 1926. The heightened transport of ^{18}F -FDG in malignant tumor cells is due to the expression of receptor-transporters (GLUT1–4), the most active of them being GLUT1. In the cell, the RP is subjected to phosphorylation under the influence of the enzyme hexokinase, with the generation of ^{18}F -FDG-6-phosphate. Due to its properties, ^{18}F -FDG-6-phosphate is not involved in the tricarboxylic acid cycle and is not ejected from the cell. In tumorous cells, the process of dephosphorylation is retarded because of low activity of the enzyme phosphorylase. Thus, conditions arise for heightened FDG accumulation in malignant tumor cells. This phenomenon has been called the “metabolic trap”. It should be noted that the level of ^{18}F -FDG accumulation in tumors does not depend on their microcirculation and on the degree of damage to the blood–brain barrier (BBB), since the RP is actively transported to cells. ^{18}F -FDG is excreted by the kidneys, consequently when the organs of the pelvis minor are visualized, technical problems arise due to the physiological uptake of the RP in the renal pelvis, urinary bladder and ureter.

^{11}C -Methionine is actively transported through cell membranes by transport proteins and is involved in metabolic processes. The non-specific tumor-seeking RP ^{11}C -methionine does not cross the BBB and is not accumulated in the intact cortex of the brain, which does not hinder the visualization of cerebral neoplasms. At the same time, high ^{11}C -methionine accumulation in most of known tumors, including benign tumors, makes it a promising diagnostic agent to be applied not only in

neurooncology but also in diagnostics of some extracerebral tumors; for example, in prostate cancer.

^{13}N -Ammonium is widely used for evaluating regional myocardial blood flow. ^{13}N -Ammonium is transported into cardiomyocytes in two ways: by means of passive diffusion of the RP in the form of a $^{13}\text{NH}_3$ solution and under the influence of K-Na-ATPase in the form of $^{13}\text{NH}_4^+$. When in cardiomyocytes, ^{13}N -ammonium undergoes some biochemical transformations: it enters the reaction with glutamine acid or with α -ketoglutarate under the influence of the glutamine synthetase enzyme and it is accumulated in the form of the compound ^{13}N -glutamine, the RP accumulation in the myocardium occurring proportionally to the level of myocardial perfusion.

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One of the crucial conditions for a successful PET examination is precise knowledge of indications, counterindications, limitations and capacities of the method as well as correspondence between the approaches opted for and the goals and objectives of the examination.

2.1 Main Tasks, Indications, Counterindications and Limitations of the PET Method

The PET method makes it possible to solve a number of tasks in oncology, such as:

1. Diagnosis and differential diagnosis of tumors of different localization
2. Determining the diffusion of the tumor
3. Determining the degree of malignancy of neoplasms
4. Evaluating tumor response to treatment, including differential diagnosis of cicatricial changes and continued growth of tumors
5. Revealing the continued growth and relapses of neoplasms

It should be stressed that the main radiopharmaceutical (RP) used in oncology is still ^{18}F -fluoro-desoxyglucose (^{18}F -FDG). The indications for using ^{18}F -FDG-PET in oncological patients are: evaluating the efficiency of treatment of malignant neoplasms, determining their dissemination (staging), differentially diagnosis of tumors as opposed to benign and non-tumor processes and to cicatricial changes.

By means of ^{18}F -FDG-PET, malignant tumors of any localization can be revealed, but not all kinds of malignant neoplasms have high glycolysis. One of the first relevant meta analysis of papers concerned with ^{18}F -FDG-PET indications for oncology resulted in the Consensus Paper “Onko PET III” in 2002. For example, neoplasms of neuroendocrine nature, neoplasms in the kidneys, prostate, stomach, and gastrointestinal tumors may have a relatively low glycolysis levels. This is why these malignant tumors are not visualized when FDG-PET is used. Among diagnostic errors (false-negative results) examples are attempts to visualize neoplasms less than 4–6 mm large (that is less than the resolving capacity of the scanner), and using ^{18}F -FDG-PET with patients suffering from disturbed glucose utilization and elimination.

Focal uptake of ^{18}F -FDG is observed in areas of inflammation (including tuberculosis, sarcoidosis, aspergillosis, pneumonias), in cases of muscle hypertonicity, in gastric motor hyperactivity, in brown fat uptake, and in disturbances of the passage of urine through the ureter, all of which can induce falsely positive conclusions regarding the tumorous nature of the visualized foci (Ruhlmann et al. 1999; Valk 2006; Khmelev et al. 2004; Phelps 2004).

The indications and limitations of the PET method are described in more detail in the corresponding clinical sections of this book. *Counterindications* to PET examinations are pregnancy and breast-feeding.

2.2 Short Description of PET Methodology

PET examinations are subdivided into static and dynamic ones. Among static examinations, whole-body examination is the distinguished method.

The PET examination procedure includes several obligatory stages: dosing and injecting RPs, positioning the patient in the gantry, transmission scanning and emission scanning. The stage sequence depends on the kind of examination and on the tasks set for it (Ruhlmann et al. 1999; Valk 2006; Khmelev 2004).

2.2.1 Methodology of PET Examination of the Brain

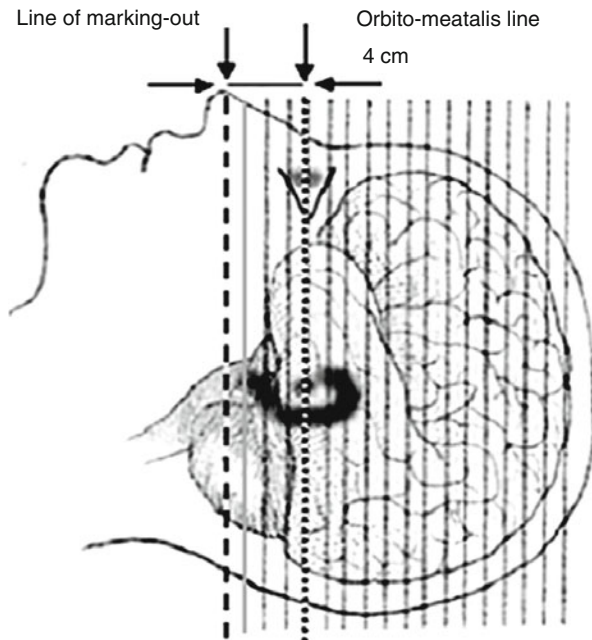
PET examination of the brain, compared with other organs, has some distinctions due to the possibility of simple and reliable fixation and precise reproduction of the head position, as well as to the necessity of the highest resolution when examining the brain.

Brain scanning usually includes four main stages:

1. Positioning the patient with head layout for the subsequent coregistration of transmission and emission scans.
2. Transmission scanning (10 min) using calibration sources of ionizing radiation (^{68}Ge) or CT.
3. Prepacking and injecting the RP.
4. Dynamic or static emission scans with subsequent reconstruction of the image.

The patient is positioned with the help of a laser optic centralizer. The orbitomeatal line (OML) usually serves as point of reference. The distance between the OML and the lower line of the centralizer may be different and depends on the axial dimension of the field of vision of the given tomograph and on the localization of the lesion area, which is determined previously by CT or MRI data. The standard position supposes that the lower line of the centralizer is pointed 2 cm below the OML (Fig. 2.1). The requirements of patient positioning are due to the limitation of the axial dimension of the field of vision in most scanners of 15–16 cm, whereas the vertical (frontal) dimension of brain is 14–15 cm. When neurooncological patients are examined, the diagnostician has often to choose between the necessity of scanning

Fig. 2.1 Standard layout and patient positioning in brain examination



all the brain segments and scanning the neoplasm that exceeds the limits of the field of vision of the tomograph in the case of standard patient positioning. As a rule, the choice is made in favor of scanning the neoplasm.

Before the emission scan, a 10-min transmission scan is done with calibration sources of ionizing radiation (^{68}Ge), or CT for attenuation correction. The effective dose in this case amounts to 0.07 mSv (for ^{68}Ge) for 10 min. Thirty to forty minutes before and in the course of 10–15 min after the injection of ^{18}F -FDG, the patient is light- and sound-proofed in order to prevent physiological RP uptake in the optic cortex. ^{18}F -FDG is introduced as an intravenous jet into a peripheral vein of the limbs in the volume of 0.5–1.0 mL 35–40 min before the onset of the static emission scanning. The diagnostic dose of ^{18}F -FDG when examining the brain is 100 MBq/m² of the body surface (or in total 150–250 MBq for an examination). The coefficient for calculating the effective dose in ^{18}F -FDG introduction is 0.019 MSv/MBq. When introducing the indicated diagnostic dose of RP, the effective dose is 2.85–4.75 for an examination. After RP introduction, the syringe is washed through with 5.0 mL physiological saline to ensure the maximum complete introduction of the required dose.

The static scan of the brain (20 min long) is carried out in 2D or 3D regimes with use of a 128×128 matrix and 1.5-times image enlargement. If quantitative analysis is needed, a dynamic scan is done, the conditions being the same as in static scanning. Dynamic scanning begins immediately after the injection of the RP and lasts 50 min.

To reduce the radiation load the urinary elimination of the tracer can be forced by additional hydration of patients following given Standardised Operating Procedures.

Sinograms are reconstructed by way of forward back projection with use of a Hanning filter and 2.5-times image zooming.

The characteristics of dosing and injecting other RPs are described in particular sections of the present handbook.

Transmission scanning of the brain can be done also after the introduction of the RP; for example, after the emission scanning. Such a sequence is called hot transmission scan. The necessity to make such an examination may be due to the patient's state of health. This sequence is used in the whole-body examination and in combined PET-MRI. However, it should be noted that in using "hot transmission" the radioactivity diffusion in the section may be distorted.

For image standardization and removal of symmetry disturbances in patient positioning it is accepted to do rotation of the obtained axial image in three projections sequentially, satisfying the following requirements, which are obligatory in brain examinations:

- The interlobar fissure in transaxial sections should be parallel to the vertical axis of the screen.
- The basal segments of the temporal lobes in coronal sections are parallel to its horizontal axis.
- The poles of the frontal and occipital lobes in the midline sagittal section are parallel to the horizontal axis.

It is accepted to keep transaxial cuts 5 mm thick, containing the whole image of the brain, so that both convexital and basal brain segments may be represented, including the cerebellum. The indicated thickness and sequence of obtaining makes it possible to confront scintigraphic brain images with stereotaxic atlases for subsequent localization of pathological formations.

PET images are interpreted according to visual and quantitative criteria. The visual analysis of images is done with use of a color scale (RGB), permitting the intensity of RP uptake in the brain to be determined, and in the areas of interest or in foci, their localization, dimensions, contours and the diffusion of the RP in the focus. PET images are compared with the results of MRI (or CT), as a rule by way of simple visual confrontation. In cases when the formation is not visualized in PET images or is not completely visualized, the criterion of choosing a region of interest in PET images is provided by MRI or CT data which are transferred and superposed onto the PET image manually or electronically. In order to perform image fusion, the method of hard- or soft-image transformation is used (Hasegawa et al. 2002).

At the second stage, the semiquantitative analysis of the image in terms of absolute and relative values is used. The so-called asymmetry index (AI) serves as a semiquantitative criterion in brain examination; it represents the ratio of radioactivity accumulated in the most active high-density area of the tumor to the cortex known to be unchanged (the region of reference).

In diffuse lesions of organs such an approach is impossible due to the absence of reference regions, therefore mathematical models have to be used. Mathematical

models suppose the dynamic type of brain scanning for calculating the input function, which is described by the curve activity/time of uptake/ejection of radioactivity in blood. In order to evaluate the level of radioactivity in the blood, it is more convenient to do measurements at the left-ventricular cavity of the left ventricle. For this reason, mathematical models are more widely used in cardiology (Roelcke and Leenders 2001; Valk 2006; Khmelev et al. 2004; Phelps 2004).

Since recently in semiquantitative analysis of the brain, a relative indicator – the standard uptake value (SUV) – has been used. SUV is a dimensionless value, defined as the ratio of specific radioactivity in the measured region (kBq/cm^3) to the amount of the introduced radioactivity per body mass (MBq/kg) (Ruhlmann et al. 1999).

SUV is automatically calculated by the software of the PET scanner during image reconstruction, with account taken of the physical half-life period of the radionuclide. When analyzing data with use of the SUV, one should remember that inaccurate information on the weight and stature of the patient, the amount of the introduced radioactivity and the time of its introduction, as well as physical “drift” of the detectors, may induce grave errors. That is why it is accepted to consider as significant a change in SUV during treatment exceeding by 25% its initial value.

The characteristics of methodology, principles of drawing and analyzing conclusions in neurooncological, neurological and psychoneurological patients are described in more detail in the corresponding clinical sections of this book.

2.2.2 Methodology of the Whole-Body PET Examination with ^{18}F -FDG

The methodology of the sequential static scans of several regions (beds) of the measured object with uniting them into one image has been called whole-body examination.

The procedure of the whole-body PET examination includes three stages: the introduction of RP, patient positioning, and transmission and emission scanning, which can be carried out in different orders: sequentially or alternately. As a rule, alternate scanning is used since it permits the reduction of inaccuracy due to the patient's displacement.

Preparation for the examination. The examination is done on an empty stomach (6-h fast). If the examination is planned for the afternoon, the patient is allowed to have an early breakfast (before 8:00 a.m.) without carbohydrates. If the anamnesis contains indications of diabetes, it is necessary to measure the level of sugar in blood before the examination in order to preclude hyperglycemia. The patient should be in a comfortable position with their eyes closed no less than 20–30 min before and 15 min after the injection of ^{18}F -FDG in order to preclude hypermetabolism of glucose in muscles; in case of examination of the neck, it is recommended to inject 1.0 mL phenazepam 30 min before the introduction of the RP in order to avoid artifacts due to muscular hypermotor activity. In order to

reduce the myocardial uptake of RP, lypolysis stimulation is done, for which caffeine-containing products are recommended (black coffee without sugar). For the purpose of reducing background activity, water load is applied, for which the patient should drink no less than 0.7 L water. When examining the region of the pelvis minor, scanning should be begun with organs of pelvis minor immediately after bladder emptying. When visualizing tumors of the abdominal cavity, intravenous injection of a spasmolytic is indicated in order to avoid artifacts due to spasms of smooth muscles of the intestines. In cold seasons, the patient bed is previously warmed with an electrical rug.

Methodology of the examination. In whole-body examination, ^{18}F -FDG is slowly introduced intravenously in a volume of no less than 5–10 mL physiological saline at 200–220 MBq/m² of the body surface. The diagnostic dose of RP in whole-body examination amounts to 300–500 MBq. The effective dose when injecting the diagnostic dose is 8.1–13.5 mSv. It is suitable to introduce the RP into the peripheric vein of a limb to rule out artifacts in the image due to the RP remaining in the site of injection. The optimum time to begin scanning varies between 60 and 120 min after the introduction of ^{18}F -FDG. Such a wide range of time of starting scanning after the introduction of RP is due to the state of the patient's metabolism and to concomitant diseases. For example, in the case of a patient below 30 years old without a concomitant pathology, scanning may start already 45–60 min after the injection of RP; whereas for a patient 60–80 years old with atherosclerosis, the examination is recommended no earlier than 90–120 min after the injection (Jadvar et al. 2003).

It is necessary to record in the report the conditions under which the examination was done: the introduced dose of RP, the time of onset of scanning after the injection, the preparation, and the particularities of the scanning regime, if there were any, in order to exactly reproduce these conditions in repeated PET examinations.

The duration of the whole-body examination depends on the capacities of the apparatus, on the patient's stature and on the clinical task. In order to evaluate the duration, the axial length of the field of vision of the tomograph should be taken into account; for example, for the. Ecat Exact 47 PET scanner by Siemens, this length is 16.2 cm, and for the Biograph mCT PET-CT scanner with the True V option it is 21.6 cm. The recommended duration of examining one region for the PET is 6–7 min. For PET-CT this value can be more than ten-times less. The maximum length of the scanner bed is more than 200 cm. However, the recommended length of the region of examination is no more than 100 cm. If a very tall patient is examined, it is recommended to divide the examination into two reports in order to avoid excessive duration of continuous scanning (within the limits of 45 min).

It is suitable to examine limbs in a special report with scanning of one region lasting no more than 5 min, which significantly reduces the total duration of the examination. This recommendation concerns only PET, since the speed of scanning in PET-CT is extremely high.

The reconstruction of sinograms is done by iterative method, the image being 1.5-times enlarged. If it is necessary to visualize formations or areas of interest situated on the surface in the case of corpulent patients, the image enlargement in repeated reconstruction of sinograms should be reduced to 1.0.

The data interpretation in whole body examination includes evaluating the image according to visual and quantitative criteria. The visual analysis of images is done in three projections using the grey scale. Using a color scale for the whole-body examination cannot be recommended. Additionally three-dimensional image analysis is done, such an image giving an idea of presence, localization and form of the focus and its correlation with other organs. The number of foci, their localization, and the intensity of ^{18}F -FDG uptake in each of them, their dimensions, contours and RP distribution are determined.

For the purpose of a more accurate anatomical localization of the focus, the PET image is compared with the results of previous structural examinations (MRI, CT, US), usually by way of simple visual confrontation. If need be, confrontation of images with different modalities can be done by stereotaxic methods.

For the right interpretation of the results, it is crucial to know the anatomy and radio-anatomy of organs and tissues, normal distribution of RPs and causes of physiological focal uptake of RP. It is most important to have a clear idea on the ways of metastasis of a given tumor – that is, on the expected localization of metastases, probability and causes of appearance of artifacts in the area under examination.

As a quantitative criterion, SUVs are used. It should be stressed that the background value of SUV is specific for each anatomic region. For example, in the abdominal cavity where intestinal hyper motor activity may be observed, the level of background activity exceeds that in the thorax. In any case, one should not ignore the presence of focal pathological uptake in the image of the patient and discovered foci necessitate verification by means of other diagnostic methods (Ruhlmann et al. 1999; Valk 2006; Phelps 2004).

In complex differential diagnostic cases, additional information is obtained by a delayed scan, which is done 2 h after the first scan and 4 h after the single injection of RP.

Delayed scanning may be used for differential diagnosis of malignant tumors. A decrease in SUV by more than 25% in 240 min after the RP injection compared with the first scan speaks in favor of the benign nature of uptake focus. Absence of significant decrease or presence of a significant increase in SUV in the lesion's focus suggests its malignant nature (Kubota et al. 2001).

A crucial task of a PET department is evaluating the efficiency of treatment. For that purpose, SUVs and dimensions of the tumor focus under examination before and after the beginning of the neoplasm therapy are compared. Absence of high RP uptake in the lesion area is estimated as a complete metabolic response to treatment. A significant (more than 25%) decrease of SUV in the tumor focus as a result of treatment is estimated as a partial metabolic response. Absence of significant changes is regarded as process stabilization, and a significant increase in SUV (more than 25%) is considered as a sign of progression of the process.

In order to obtain significant SUVs, as precise a reproduction as possible of the conditions of the previous examination of the patient is required. It should be noted that the interpretation of therapy results is possible without PET data obtained before the onset of treatment, but in this case it is not possible to differentiate a partial response or process stabilization without initial data.

The methodology of PET examination is specific for each patient. For example, the introduced dose of RP depends on the volume of circulating blood and is calculated individually. Planning of a PET examination begins from the moment of signing up for the examination. For example, when tumor dissemination in melanoma patients is examined, a whole-body scan may be needed, while in head and neck cancer the neoplastic dissemination is limited to one anatomic region. The moment of starting scanning after the injection of RP is strictly regulated, but in fact the level of ejecting ^{18}F -FDG from the organism depends on the patient's age and the presence of concomitant diseases such as diabetes, sclerosis, kidney malfunctions, etc., which should be taken into account when planning the examination of the patient (Fitzpatrick et al. 1998; Ruhlmann et al. 1999; Valk 2006).

The added information shows that preparation for examination, the introduced dose, total duration and the time of starting PET scanning, as well as direction of movement of the scanner bed, depend on a particular clinical task. Therefore, particular characteristics of PET examinations are described in more detail in the corresponding clinical sections of this book.

2.3 The Principles of Coregistration of Multimodal Images

Methods of nuclear visualization have a relatively low space resolution and are of a functional character. For these reasons, when analyzing PET data there may arise difficulty in localizing the discovered foci and in determining the boundaries of the pathological process. In order to solve this problem, fusion of functional PET images with images reflecting the structure of the object under examination (obtained by means of MRI or CT) is needed. Image coregistration obtained by the mentioned radiodiagnostic methods provides a comprehensive idea on the structural and functional state of the determined anatomic region, which significantly increases the information value of the examination (Hasegawa 2002; Townsend and Beyer 2002).

2.3.1 Methodological Aspects of Image Coregistration

Most researchers distinguish two kinds of coregistration technologies: prospective and retrospective ones. Prospective methods are based on the registration of exterior markers set on the patient's skin or on a fixing mask. Geometric image transformation is done with consideration of the spatial position of markers. The accuracy of coregistration when using the prospective method depends on the features of data collection, such as the width of the cut, the patient's position on the scanner bed, etc. One disadvantage of the prospective method is its laboriousness and difficulty in patient positioning.

Retrospective methods do not require using exterior markers since the characteristics of the image itself change: pixel size, contours, and gradients. Different anatomic structures are used as the so-called interior markers. It should be noted that retrospective methods of image coregistration are simpler and do not depend on

data collection; however, their accuracy compared with prospective methods is lower. Retrospective coregistration may be carried out with help of automated algorithms or without them. In the former case, the retrospective coregistration software is a set of utilities as a menu with contours or cursors permitting to determine which images can be precisely fused to a maximum.

A variant of coregistration without automated algorithms is software permitting to choose two corresponding points in multimodal images with subsequent calculation of the necessary parameters of their geometrical transformation. The accuracy of automated coregistration is rather high, although it yields to the corresponding indicators of the prospective method and of the “manual” retrospective coregistration of multimodal images. That is why most authors recommend visual control after the data fusion done with automated algorithms.

A simple way of coregistration is superposing the contours of the region of interest; for example, those of the area visualized in PET on the corresponding MRI or CT image. This way of fusion enables the spatial position of the lesion area to be assessed. However, in this case it is not possible to precisely evaluate the ratio of structural and functional changes in the region of interest.

A more complex but highly informative method is coregistration of multimodal images themselves. In this case, one important condition of high fusion accuracy is their adequate geometric transformation. Two kinds of geometric transformation of objects are distinguished: hard and soft ones. In hard transformation, all the distances between the chosen points inside the object remain intact as well as all the angles between the straight lines of the image. In other words, in hard geometric transformation only several variants of change in the spatial position of the image are possible: shifting and revolving along three coordinate axes (X , Y , and Z). The approximation of reference points in hard image transformation by the method of minimum deviation squares has been called “Procrustes problem”. Two configurations (N) of points in space D ($P = \{p_i\}$ and $Q = \{q_i\}$). Then transformation (T) is carried out, which minimizes deviation squares of P from Q .

Scaling of objects – that is their bringing to the same size – is possible. Hard transformation is used also in order to correct image distortions appearing during data collection. In this case it is used as a stage preceding retrospective fusion of multimodal data. It must be stressed that image coregistration with their hard geometric transformation requires precise correspondence between points in the selected images. In practice, it is realized only when using the prospective method of fusion (Fitzpatrick et al. 1998). However, even in this case using hard image transformation is not always possible. Often there is a geometric distortion of one object with respect to another. Some distortion is induced by different space resolution of multimodal images, first of all between MRI or CT images and PET data. In this case, one has to apply the soft geometric transformation of objects in which there occurs an additional distortion of images relative to one another.

A simple way of soft image transformation is the so-called affine transformation. In this case, the straight lines inside the object and the surface flatness are intact but nonzero angles between lines change. Using this transformation is possible, for example, in case of difference of the plane of transverse sections between multimodal

images owing to a wrongly chosen angle of inclination of the scanner gantry. A more complex kind of soft geometric transformation is curved geometric image transformation, in which straight lines and surface plane do not remain intact. This kind of geometric object transformation significantly simplifies the task of registration of multimodal images. This has a particular significance in fusing images of mobile organs such as intestine, as well as after surgical operations when interrelation between anatomic structures is sharply disturbed. Curved geometric transformation is a method of choice in registration of standardized images of the corresponding anatomic region. For example, fusion of images from the Talairach atlas and those of the patient's brain when planning stereotactic treatment. A disadvantage of soft transformation consists in the error induced by it when fusing multimodal images. The value of this error is directly proportional to the degree of mutual distortion of images. Consequently the prospective method with marker coregistration and hard transformation still remains the "gold standard" of fusing multimodal images.

In order to evaluate the accuracy of fusion in registration of multimodal images with use of markers, the following indicators are presently applied.

Marker localization error [fiducial localization error (FLE)], which reflects the displacement of markers relatively to their real position.

The FLE value is calculated by the following formula:

$$\text{FLE}^2 = \delta_x^2 + \delta_y^2 + \delta_z^2 \quad (2.1)$$

where $\delta_x^2, \delta_y^2, \delta_z^2$ are values of displacement of the marker along the axes X, Y and Z correspondingly.

FRE shows the displacement of markers in the images after their geometric transformation and fusion. The value of FRE is calculated by the formula:

$$\langle \text{FRE}^2 \rangle = \left(1 - \frac{2}{N} \right) \times \langle \text{FLE}^2 \rangle$$

where FRE is fiducial registration error, N is the number of fiducials and FLE is fiducial localization error.

Target registration error (TRE) is an indicator reflecting the accuracy of fusion in the immediate region of interest.

From this definition of TRE, it follows that this index can be presented as $TRE = c - c^l$, where c and c^l are points corresponding to each other in the images being fused. The approximate value of TRE is calculated by the formula:

$$\langle \text{TRE}^2(r) \rangle \approx \frac{\langle \text{FLE}^2 \rangle}{N} \left(1 + \frac{1}{3} \sum_{k=1}^3 \frac{d_k^2}{f_k^2} \right)$$

where N is the number of points, k stands for the main axes of coordinates, f_k is the root mean square deviation of fiducials along the main axis, d_k is the deviation

of the target r along the main axis. The first part of this equation reflects the error of displacement of images, the second one reflects the error of their rotation. This indicator can be calculated directly when registering multimodal images as the residual distance between a pair of corresponding points in the region of interest excluded from the process of fusion after the approximation of reference points (Pernus et al. 2001). In other words, fiducials corresponding one to another in the multimodal images and excluded from the process of registration are used as target. This method of determining the value of TRE is more accurate than calculating this error by the mathematical method.

As was said before, FLE, FRE and TRE are the main indicators of the accuracy of image fusion. At the same time, many authors demonstrate that TRE has the most significance for determining the precision of registration of multimodal images.

Some authors have suggested using the Wang-Bovik index for evaluating the quality of image coregistration. However this index has not received wide use, since its calculation requires using complex mathematical apparatus and is not quite justified in clinical conditions.

At present, special attention is given to the development, manufacture and introduction into clinical practice of combined systems including different scanners. Much interest in combined systems is accounted for by the relatively low resolving capacity of functional visualization methods, which do not permit to distinctly image anatomic structures. A combined system was created for the first time in 1991 (Hasegawa et al. 2002). It was a combination of a CT scanner and a gamma camera. Hasegawa and coworkers and (sometime later) Lang and coworkers used highly purified germanium as common detectors for CT and SPECT. Radiation generated by the X-ray tube of CT is used for attenuation correction when combined with PET or SPECT data. A shortcoming of this system is the relatively low quality of images due to using common detectors for both scanners. Afterwards, systems without common detectors were developed, in which X-rays were also used for attenuation correction and for partial bulk effect. In 2000, in Pittsburgh a group of scientists created the first combined PET-MRI scanner. These systems are distinguished by using the X-ray tube of the computer tomograph for transmission scanning as well as by capacity for accurate fusion of CT and PET images.

Modern combined scanners are provided with multilayered (6–128 detector rows) CT with high speed of rotation of the X-ray tube (up to 370 ms). This permits to significantly decrease the duration of the examination, from 45 to 60 min in PET to 15–20 min in PET-CT. Such a scanner provides a high precision of fusion of CT/PET images (less than 1 mm) (Townsend and Beyer 2002). At the same time, isotropic space resolution for a computer tomograph may reach up to 0.4 mm. At present a number of medical equipment manufacturers produce combined CT-PET systems. The widest spread combined systems are Biograph (Siemens), Discovery (General Electric) and Gemini (Philips). The PET scanner in these systems is equipped with ultra-fast detectors made of LSO or LSO with cerium admixture, LYSO. The scintillation time of LSO detectors amounts to some 40 ns. This permits the duration of data collection in the whole-body regime to be decreased compared with traditional PET scanners from 25 to 10 min, the quality of images being

comparable. These systems provide three-dimensional scanning and enable up to 81 image planes to be obtained in an axial field of vision of up to 21.6 cm.

Presently, research is being done aimed at developing a combined PET-MRI scanner. However, the presence of metal parts in the frame of the PET scanner, as well as high sensitivity of photomultiplying elements of scintillation detectors to the magnetic field, significantly hinders the development of these apparatuses. Nevertheless in present PET/MR units dedicated to brain examination and whole body studies as well have found their way to clinical practise. A consistent list of indications and procedure routines will depend on the velocity of publications.

2.4 Work Organization of the PET Diagnostic Department

The structure of a exemplary PET diagnostic department is presented in Fig. 2.2. It is clear from Fig. 2.2 that the PET department differs from routine radionuclide laboratories in the presence of additional treatment rooms, owing to long patient preparation for whole-body examination.

Due to the short half-life periods of USLRs, there is no need to store radioactive wastes in the PET department. To determine the time needed for storage of radioactive substances, the half-life period of a given radionuclide is multiplied by ten. In the RP movement register, the time of depositing and the time of taking out radioactive wastes is recorded, on the expiry of which they can be transferred to the washing room for subsequent decontamination and then thrown to refuse.

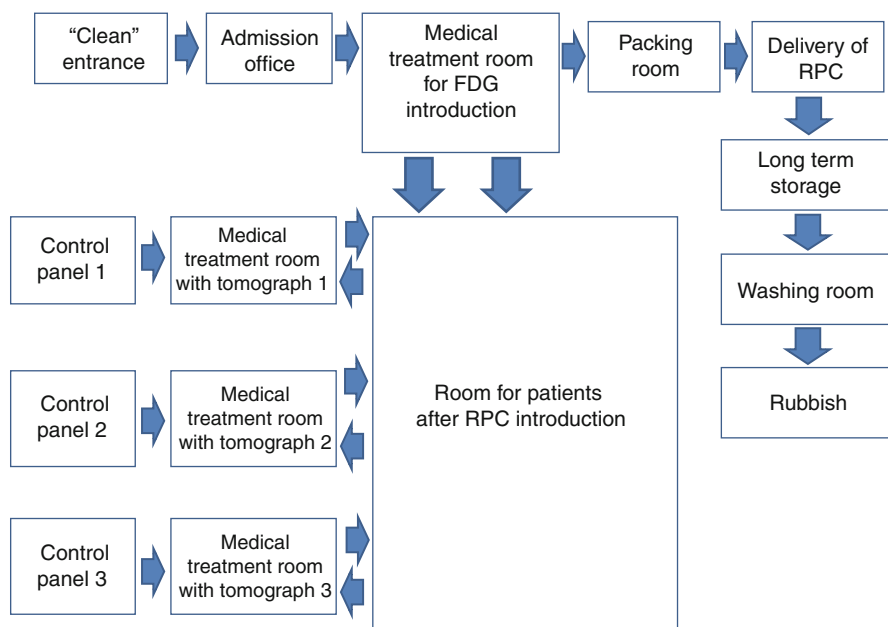


Fig. 2.2 Structure of a standard PET department

Table 2.1 Approximate list of equipment of a PET Center

No.	Description of equipment	Number of items
1.	PET scanner	2
2.	PET-CT	3–5
3.	Dose calibrator (Curie meter)	2–3
4.	Glucometer	3–4
5.	Hood for prepacking RP	2–3
6.	Waste storage safety box	1–2
7.	Electric stirrer	1
8.	Centrifuge	1
9.	Lead protective boxes	6–8
10.	Safety box for storing calibration sources and phantoms	1–2

Additional equipment of the PET diagnostic department depends on the tasks set for it and determines its capacities.

It should be particularly stressed that one cyclotron complex can serve several scanners and even several PET departments. The practice of delivering RPs from one large cyclotron complex to several different PET centers is broadly used worldwide. At the same time, transporting RPs and labeled USLRs for long distances is economically unsuitable since it brings about big losses of radioactivity. An economically justified structure of a PET center requires the use of several (two to six) scanners around one cyclotron complex.

The list of main equipment of a PET department is presented in Table 2.1. Besides the equipment enumerated there, the PET department may include equipment used for patient preparation for the examination, furniture made of weakly absorbing materials, a medicine kit in case of resuscitation measures, means for personnel radiation protection, kits for radiation security posts, etc. Additional demands are made to equipping neurological, cardiological and mixed purpose departments, which must be provided with equipment for carrying out corresponding functional tests.

The staff list of a PET department depends on its equipment and tasks. If there is one PET scanner, the department needs no less than two radiophysicians, two nurses, one technician and one programmer-engineer. If there is a PET-CT, there should be one radiologist with CT work experience. If the department has a mixed profile and cardiological examinations are expected, it is appropriate to include also a cardiologist in order to prepare patients and to do stress testing.

2.4.1 Characteristics of PET Examination Organization in Oncological Clinical Practice

Organization of examinations in modern oncological practice has a number of distinctions. For preparation for a whole-body examination, the patient should stay at rest in the treatment room (lying on a couch) for no less than 30–40 min before and

15 min after the introduction of the RP. If there is only one treatment room and that treatment room has been occupied by the first patient for at least 30–40 min, it is impossible to provide conditions for introducing RP to a following patient during that time. That is why the first requirement to the structure of an oncological PET department is having no fewer than two treatment rooms for one scanner. It should be noted that even when using ^{18}F -FDG, where fluorine-18 has a half-life period of 109 min, the consumption of the expensive diagnostic can be mainly due to losses caused by half-life decay of the radionuclide rather than due to injecting the RP into the patient.

That is why the organization of the patient group and the structure of the PET department is of utmost importance for reasonable working of the department. For example, the time from the moment of ^{18}F -FDG introduction to the onset of whole-body scanning varies within the range of 60–120 min, whereas in case of examining the brain or myocardium it amounts to 35–40 min. When introducing RP simultaneously into two patients, in one case for whole-body examination, in the other for examining the brain or myocardium, there remains a 50- to 80-min stretch of time between the two examinations. This time may be used for examining the myocardium or brain. Such a use of RP seems to be more reasonable compared with examining a homogeneous group of patients.

The duration of the whole-body scan may vary, depending on the patient. When planning the schedule, additional intervals between examinations have to be provided for, which leads to unjustified losses of RP; however, it is impossible to foresee in advance the necessity of performing a delayed scan and to provide for it in the schedule. To solve this problem it is appropriate first to examine patients with verified diagnoses sent for treatment efficiency evaluation. Such patients do not need delayed scanning. It is reasonable to examine last those patients sent for an initial diagnosis of neoplasms, since many of them may need an unplanned delayed scan (Ruhlmann et al. 1999; Valk 2006; Khmelev et al. 2004; Phelps 2004).

It is not always possible to make a schedule of examination in advance since the precise value of radioactivity of an ^{18}F -FDG batch may vary depending on a given synthesis. At the same time, making a schedule of examinations after having measured the radioactivity of a ready-to-use RP (under conditions of time limitation) requires special training of the personnel or appropriate software.

The characteristics of PET examinations in a PET department are presented in Fig. 2.3. Generally, the character of examinations is comparable in different institutions and in different countries and ^{18}F -FDG-based whole-body PET examinations prevail.

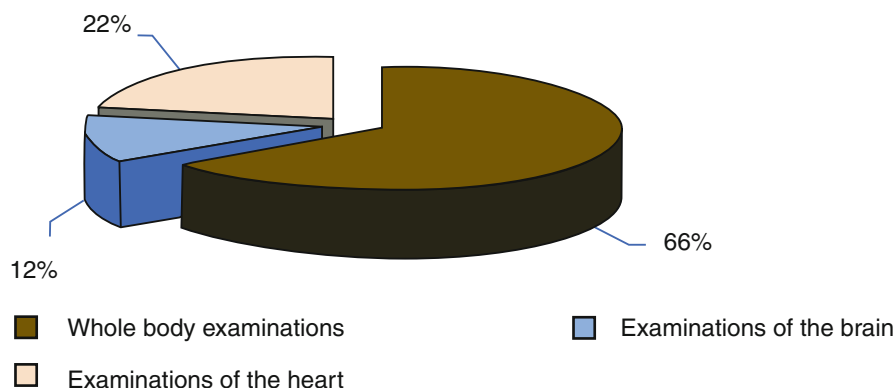


Fig. 2.3 Character of PET examinations: FSF, RSCRST Rosmedtechnologies, Saint Petersburg (Russia)

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Part II

PET in Diagnostic Oncology

3.1 Planocellular Cancer of the Head and Neck

According to statistics, every year more than 35,000 cases of planocellular cancer of the head and neck are registered (Forastiere et al. 2001). Head and neck cancers make up about 5% of the total number of tumors, planocellular cancer being the widest-spread histological subtype. Smoking and other ways of consuming tobacco as well as alcohol consumption increase the risk of developing this kind of cancer. Planocellular cancer of the head and neck (PCHN) has specific development stages for every anatomic region in the larynx, buccal cavity, oropharynx, hypopharynx, nasopharynx and paranasal sinuses. More than 50% cases of this kind of cancer appear in the oropharynx, especially on the palatine tonsils and at the base of tongue. Currently about 60% PCHN patients have developed local manifestations and undergo treatment with surgical intervention, radiotherapy, chemotherapy or a combination of these kinds of treatment (Forastiere and Urba 1995; Forastiere 1994).

In patients with head and neck tumors 5-year survivability reaches 60% in absence of metastases, in case of metastatic lesion it is 30%. Five-year survivability for patients with locoregional tumor dissemination undetected when making diagnosis amounts to 30% for all cases of neck and head cancer. In order to make a decision on the choice of treatment or/and to determine long-term prognosis, the correct and timely staging of primary tumors is needed (Bhattacharyya et al 2005).

Staging of head and neck cancer (HNC) is done according to clinical signs and is specific for each affected region of the head or neck. The clinical approach to staging is based on the most precise assessment of the disease dissemination before treatment. For all the regions of the head and neck, except for the thyroid gland, a common classification system of regional lymph nodes is used (Table 3.1).

Diagnosis of the primary tumor is mainly based on visual examination, palpation and endoscopy in less accessible areas such as the larynx. Corresponding regions of lymphatic drainage are subjected to careful palpation. Besides that, information is used in HNC staging obtained by imaging methods (MRI, CT) and necessary for detecting and localizing head and neck tumors as well as for differentiating lymph nodes from surrounding soft tissues and blood vessels and determining the

Table 3.1 Classification of regional lymph nodes

NX	Regional lymph nodes are unassessable/were not assessed
NO	No metastases to regional lymph nodes
N1	Tumor dissemination to one lymph node with diameter less than 3 cm on the side of lesion
N2	(a) Tumor dissemination to one lymph node with diameter more than 3 cm but less than 6 cm on the side of lesion (b) Tumor dissemination to several lymph nodes with diameter less than 6 cm on the side of lesion (c) Tumor dissemination to one or several lymph nodes with diameter less than 6 cm on both sides of the neck or on the contralateral side
N3	Tumor dissemination to lymph nodes with diameter more than 6 cm

dimensions, structure and contours of solid mass (structural tomographic visualization). However, none of these technologies permits the detection of persistent or recurrent cancer (Stern et al. 1990).

Precise initial assessment of the primary tumor and of the state of lymph nodes is crucial. Early detection of relapsing neck and head cancer with subsequent adequate treatment may induce a decrease in volume of surgical intervention and help prevent disability as well as achieve the optimum clinical outcome. Until recently, such a possibility was based only on the combination of clinical assessment and anatomic visualization (CT or MRI). At present, besides clinical and radiologic methods, PET technology is used as well. Its role in staging and observation of neck-and-head cancer patients keeps growing (Reske, Kotzerke 2001).

3.1.1 Clinical Use of PET and PET-CT in Head and Neck Cancers

^{18}F -FDG PET has a number of clinical advantages over CT and MRI as far as PCHN diagnosis is concerned.

3.1.1.1 Diagnosis of Primary Tumors

The diagnosis of the primary tumor and assessment of its dissemination to adjacent tissues and structures constitute an important clinical task. This problem is solved by means of physical examination and standard anatomic visualization with use of CT and MRI, which are quite sensitive when detecting primary tumors (67–88%), even though they are less specific (50–75%). ^{18}F -FDG PET has roughly the same sensitivity (71–95%) but its specificity is higher (67–100%) (Stokkel et al. 1998).

3.1.1.2 Assessment of the State of Regional Lymph Nodes

Tumor affection of lymph nodes has a negative impact on survivability. In the case of their metastatic affection it is necessary to change the tactics of treatment. The percentage of false-negative results in palpation reaches 5–44%, and false-positive results make up 13–25% (Ali et al. 1985). When detecting the infiltration of lymph nodes, the conventional visualization is characterized by a high variability of the levels of sensitivity (from 36 to 95%) and of specificity (from 58% to 97%) (Braams et al. 1995). When CT or MRI is used, diagnosis of affected lymph nodes is based on measuring their dimensions. The point of reference is the upper limit for

unaffected nodes which is 1.0–1.5 cm. In this way benign and malignant alterations are differentiated. This approach has its shortcomings. For example, lymph nodes significantly enlarged in diameter and nodes with complex structure may reflect a reaction to processes of non-tumorous nature (inflammation), whereas small lymph nodes may well contain tumor cells. It has been proved that more than 40% metastases are situated in lymph nodes whose size is below 1 cm. When using routine methods of visualization (MRI, CT and US) they are often overlooked.

Since PET is a metabolic tool, it permits the detection of lesions in small nodes and lesions in enlarged nodes with the additional option of quantification by means of SUV. The SUV level seems to be a predictive factor for overall survival as first study reports implicate (Kubicek 2010). Basing on available data, ^{18}F -FDG PET can be stated to significantly exceed in sensitivity (70–100%) and in specificity (84–100%) the standard methods of radiological visualization (MRI, CT, US) as regards diagnosing metastases to lymph nodes.

3.1.1.3 Primary Tumor of Unknown Localization

Diagnosis of latent primary tumor is made only if the primary tumor is not found by careful complex patient examination and is not detected in the therapy process. In head and neck cancer, malignant affection of lymph nodes in the absence of the primary focus of the disease is observed only in 2% of cases. However, all of these cases present an important aspect in treating tumors of this localization. The rate of 3-year survivability without relapses after surgical intervention and/or radiotherapy with unknown primary focus ranges from 40% to 50% for patients in stage N_1 , to 38% in stage N_2 and to 26% in stage N_3 . For patients in whom primary tumors are subsequently detected the survivability rate is lower than for patients with primary focus remaining unknown. High sensitivity of PET makes this method inestimable for examining these kinds of patients. It has been established that PET permits detection of the tumor focus for the first time in 40–60% of cases (Fig. 3.1) (Jungehulsing et al. 2000; Kole et al. 1998).

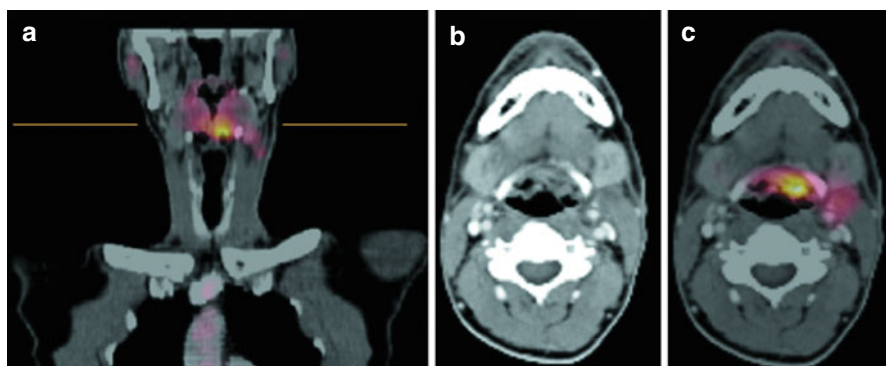


Fig. 3.1 (a–c) ^{18}F -FDG PET-CT. Primary tumor at the base of the tongue on the left. Neck lymphadenopathy. Histological examination of an enlarged neck lymph node detected its lesion by metastases of planocellular cancer. (a) Fused ^{18}F -FDG PET-CT image (*coronary cut*). (b) CT image (*axial cut*). (c) Fused ^{18}F -FDG PET-CT image (*axial cut*). ^{18}F -FDG PET-CT (c) detected a focus of hypermetabolism of glucose in the tongue base, $\text{SUV}=6.6$. PET-CT data are estimated as indication of tumor lesion. Other metastases were not detected

Unfortunately, in spite of progressing development of radiotherapy and chemotherapy and of surgical treatment, the rate of survivability of patients with planocellular cancer of the head and neck has not improved over the last two decades (Vokes et al. 1993). One of the negative factors having a significant impact on the level of survivability of PCHN patients is the development of primary multiple tumor lesion in the area of the head and neck. The risk of occurrence of a second primary tumor for patients recovered from PCHN is 30% and more during the rest of their life. In 10% patients with primary PCHN, a second synchronous tumor in the area of the head and neck may be detected. The detection of these tumors as well as that of metastases plays an important part in further therapy (Wax et al. 2002).

The advantage of ^{18}F -FDG PET over other methods is the possibility of whole-body scanning, which is impracticable or inefficient when using other visualization methods. Whole-body examination by means of ^{18}F -FDG PET permits the detection of a second parallel tumor and metastases to other organs. Stokkel et al. (1998) reported that ^{18}F -FDG PET permitted the detection of a second parallel tumor in 17.6% of cases of primary head and neck cancer that had been overlooked in clinical and tomographic examination. Goerres et al. (2003) noted that in 14.4% of cases of planocellular cancer of the buccal cavity PET results had an impact on the schedule of therapeutic steps.

3.1.1.4 Treatment Efficiency Control and Relapses

Patient examination after HNC treatment is more complex than the one before treatment. The medical treatment, be it surgical intervention, radiotherapy or chemotherapy, may lead to the alteration of anatomic structures of the affected region. In order to identify a relapse, post-therapy changes and cicatrices, surgical biopsy is often needed. However, biopsy in the region subjected to treatment is invasive and may induce complications. As for metabolic PET visualization, it permits to differentiate with high precision post therapy alterations and relapsing cancer. Collins with coauthors have shown that combined use of fine needle biopsy and ^{18}F -FDG PET helps reach 94% sensitivity in detecting relapsing head and neck cancer (Collins et al. 1998). Other research shows that using ^{18}F -FDG PET alone in detecting relapsing head and neck cancer yields more than 90% sensitivity (Zhuang et al. 2004).

3.1.1.5 Additional Capacities of PET-CT

In spite of its high sensitivity PET suffers from insufficient accuracy in determining the anatomic localization of radiopharmaceutical (RP) uptake foci. ^{18}F -FDG is accumulated, besides in tumors, also in the muscles and in areas of inflammatory changes as well as in some metabolically active organs (palatine tonsils and salivary glands). Therefore PET may give inaccurate information on the precise site of pathological uptake foci. In the head and neck area such inaccuracy may provoke the wrong detection of tumor at the base of the tongue and adjacent tonsillar mass or hyperchordal affection of the larynx and of the vocal chords. The limitations of using each of the visualization methods (CT or PET) can be overcome if they are used in combination. Anatomic high-resolution information provided by CT completes data on tissue characteristics obtained by means of PET. PET-CT data co-registration unites functional and anatomic kinds of visualization into one whole,

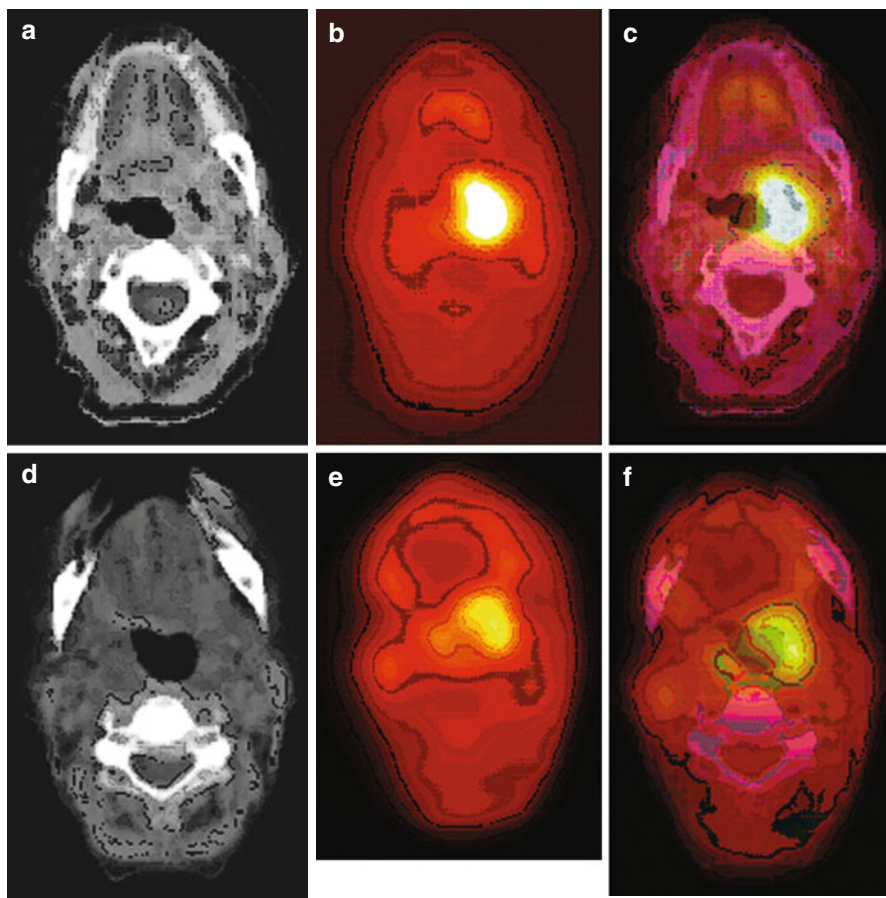


Fig. 3.2 ^{18}F -FDG PET-CT in planocellular head and neck cancer. Carcinoma of the palatine tonsil on the left. (a) Asymmetry of anatomic structures observed in CT – a displacement to the right due to a volumetric formation in the projection of a palatine tonsil. (b) ^{18}F -FDG PET detects a focus of hypermetabolism of glucose in the area of the soft palate on the right (SUV=6.6). (c) In a coregistered PET-CT image there is a coincidence of the focus of metabolism and volumetric formation. After surgical and radiological treatment relatively lowered RP uptake in the area of cicatricial alterations is determined. In CT (d) and ^{18}F -FDG PET (e) images on the same level, restoration of anatomic geometry of the oropharynx and a 2.7-times SUV decrease are detected. (f) In a fused ^{18}F -FDG PET/CT image the focus of hypermetabolism of glucose partially coincides with the area of perifocal oedema and inflammatory infiltration

both information sources being equally important. Such a result is achieved owing to the combination of data of different modalities, integration of separate PET and CT visualization results into one whole by means of their fusion.

PET-CT apparatuses permit additional data to be obtained on the staging and restaging of cancer, prognosis of clinical course and treatment efficiency assessment (Fig. 3.2). The advantages of PET-CT include a more accurate localization of foci

by means of anatomic-functional registration approaching the ideal with fewer motor artifacts, better differentiation between physiologic and pathologic uptake, and shorter duration of scanning due to CT data for attenuation correction (Schoeder 2004). The latter circumstance contributes to the patient's comfort and helps solve the problem of claustrophobia.

So, diagnosis and posterior observation in planocellular carcinoma of the head and neck are usually based on clinical examination and anatomic visualization by means of CT or MRI with contrast enhancement. Yet, as useful as these methods are for assessment of suspicious regions, they do not always permit the detection of differences between residual and relapsing tumor as well as those between inflammatory and post therapy alterations. It has been proved that ^{18}F -FDG PET may be successfully used for detection and staging of the primary or recurrent planocellular cancer of the head and neck. PET also has shown its efficiency in diagnosing primary tumor foci of unknown localization and in controlling subsequent surgical and other treatments of HNC. The introduction into clinical practice of combined PET-CT scanners has increased the information value of visualization methods for clinicians engaged in treatment of the head and neck cancers.

3.2 Thyroid Cancer

Clinically detected carcinoma of the thyroid gland makes up only 1% of all the cases of malignant tumors. Its annual primary diagnosis in different regions of the globe ranges from 0.5 to 10 cases per 100,000 of the population. In spite of the fact that this pathology is not so frequent, thyroid carcinoma rivals in prevalence with multiple myeloma, it occurs twice as often as Hodgkin's lymphoma and is comparable in frequency with tumors of the esophagus, larynx, buccal cavity and neck of uterus. Moreover, this is the most frequent endocrine malignant formation which causes more deaths than all the rest of endocrine cancers taken together (AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma 2001).

According to the American Cancer Society, in 2003 up to 22,000 new cases of thyroid cancer (TC) were detected in the USA, which made up 90% of all endocrine cancers. TC is more frequently found in women than in men, the ratio being 3.2:1. A permanent increase in number of new TC cases has been observed (Jemal et al. 2007). Survivability is rather high with adequate treatment. The estimated number of people who survived more than 40 years after the diagnosis is 190,000 (AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma 2001). Thyroid carcinoma usually originates from follicular cells, but one rare kind of medullary carcinoma develops from parafollicular or C-cells. We know four histological types of thyroid cancer originating from follicular cells (AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma 2001). The most frequent of them is papillary cancer (80%). Follicular cancer makes up 10% of cases. B-cell, oncocytic tumors and anaplastic cancer make up 5% each. Papillary

and follicular carcinomas are usually considered to belong to differentiated thyroid cancers. A typical papillary carcinoma is a unilateral focus in the thyroid gland. As a rule, in this form regional lymphatic dissemination is observed. Metastases to lymph nodes detected in the primary diagnosis increase the risk of a subsequent relapse.

Follicular carcinoma is another frequent kind of thyroid cancer; usually it consists of nodes which do not transcend the boundaries of the gland capsule. It rarely disseminates to lymph nodes, but it can bring about deposits to lungs and bones due to hematogenous metastasis. B-cell carcinoma is considered as a subtype of follicular thyroid cancer and has a similar course. Anaplastic carcinoma, sometimes called undifferentiated thyroid cancer, is a rare form which is believed to develop in consequence of existing papillary or follicular cancer being transformed. Its course is very aggressive and rapid with distant metastases, and it often results in a lethal outcome. Medullar thyroid cancer cells, unlike those of papillary and follicular cancers, do not secrete thyroid hormones, this form of cancer being associated with hyper-production of calcitonin and carcino-embryonic antigen (American Cancer Society-Thyroid Cancer 2007).

On the whole, in the case of differentiated thyroid cancer patients with small tumors (<2 cm), women, in the absence of both local dissemination and distant metastases, have a good prognosis with low risk of relapses and lethal outcomes. Metastasis to lymph nodes of the neck as an independent prognostic factor can be associated with a high frequency of relapses, and bilateral affection of the neck or involvement of the mediastinum have an impact on bad general prognosis (AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma 2001).

Most patients with thyroid cancer have a palpable solid mass in the area of the neck, which can represent both the primary tumor in the gland itself and a metastatic regional lymphadenopathy. However, in some patients the tumor may not have clinical manifestations, and the non-palpable focus is first detected either during examination with high-resolution visualization methods or during a surgical operation on a benign disease of the thyroid gland. Family anamnesis of medullar thyroid cancer or of the syndrome of multiple endocrine neoplasia of the second type, detection of a RET-oncogene mutation, of high level of calcitonin or both can induce implementation of a prophylactic thyroidectomy in patients with high risk of early medullar thyroid cancer, which will be detected only by a histological examination (AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma 2001).

Thyroid cancer diagnosis requires a morphological confirmation when examining both cytologic and histologic materials. Fine-needle aspiration biopsy is the most efficient available method of differential diagnosis of thyroid nodes and of assessment of the degree of malignancy. Nevertheless, in each particular case diagnosis should be verified by the histological examination of the operation material.

Differentiated thyroid cancer is considered to be rather curable, because after an efficient surgical resection of the primary tumor with subsequent ablative therapy with radioactive iodine it is possible to apply control of the thyroglobulin rate of blood serum as an extremely sensitive method of relapse detection.

Most thyroid cancer patients first undergo surgical treatment. The goal of the first stage is an adequate excision of the primary tumor and of any foci of locoregional dissemination. Due to high risk of relapses after unilateral hemithyroidectomy as well as to that of hypoparathyreosis after total strumectomy, subtotal thyroidectomy is initially implemented. Almost all patients receive everyday substitutive hormone-therapy. For cancers deriving from follicular cells, this kind of therapy is based on taking peroral supraphysiological doses of levothyroxin for the purpose of complete suppression of secretion of the pituitary thyroid-stimulating hormone (TSH) down to its basal level in blood serum <0.1 IU/L. This implies that the suppression of TSH secretion by hypothesis oppresses TSH-dependent growth of cells of differentiated follicular cancers (AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma 2001).

The second most frequently used kind of post-operation therapy for follicular cancer patients is radioablation using an isotope of iodine. This kind of therapy has three main tasks:

- To destroy occult micro-accumulations of carcinoma cells in the residual tissue of the thyroid gland as well as to destroy distant metastatic lesions.
- To destroy the remains of normal tissue of the thyroid gland, especially in the area of the neck, so that any high uptake focus in the scan may be explicitly considered as a prolapse or a relapse of the disease during subsequent observation.
- To ensure monitoring during the observation period by tracking the level of TSH, whose value should not exceed 10 ng/mL if the radioiodine ablation destroyed the whole of (or almost) the parenchyma of the thyroid gland remaining after the operation.

In order to carry out these tasks it is necessary to raise the TSH level at least up to 30 IU/L, which can be done either by cancelling substitutive therapy with thyroid hormones or by means of parenteral introduction of recombinant human TSH. Patient preparation by way of introducing exogenous TSH is diagnostically equivalent to the cancellation of substitutive therapy both for detecting the TSH rate and for whole-body scanning with isotope of iodine (Bobbins et al. 2001; Petrich et al. 2001; Robbins et al. 2001).

A high TSH rate stimulates the normal tissue of the thyroid gland and differentiated thyroid cancer tissue to a higher radioiodine uptake and to a bigger secretion of TSH (Menzel et al. 2004). For radioiodine-negative tumors, the effectiveness of therapy with retinoic acid and its derivatives has been proved, which restores the capacity of cells to uptake radioactive iodine due to their redifferentiation (Grunwald et al. 1998). External irradiation is also used during the post-operation period in tumors not accumulating radioactive iodine (anaplastic carcinoma of the thyroid gland, lymphoma and secondary malignant tumors). Measuring the TSH rate in blood serum is still the most sensitive method of detecting relapsing or metastasizing differentiated thyroid cancer. Most differentiated thyroid cancer cells secrete TSH, even if they do not accumulate radioactive iodine. TSH secretion grows with increase in number of the differentiated tumor cells. A TSH level higher than 10 ng/mL is associated to the presence of metastases in more than 85% of patients who have undergone the maximum possible surgical removal of the thyroid parenchyma

and in whom its remains have been destroyed during subsequent radioiodine ablation (Mettler and Guiberteau 1998). Auto-antibodies to TSH remain a serious obstacle for the wide use of TSH determination in clinical practice (Menzel et al. 2004). In patients with levels of TSH below the threshold of determination, permanently heightened levels of antibodies to thyroglobulin may serve as indicator of relapse or of residual differentiated thyroid cancer (Chung et al. 2002). It should be noted that levels of TSH measured by the method of enzyme-linked immunosorbent assay (ELISA) (from 0.03 ng/mL) are more precise than those measured by immunoradiometric analysis (IRMA) (from 0.6 ng/mL) (Wunderlich et al. 2001).

3.2.1 Scintigraphical Assessment of Differentiated Thyroid Cancer

Since differentiated thyroid cancers make up the majority of malignant thyroid tumors and because of their property to almost always accumulate isotopes of iodine, radioiodine whole-body scintigraphy (WBS) is the main primary method of visualization of relapses and metastases of differentiated thyroid cancer. WBS has a very high specificity (99%) but a relatively low sensitivity (within 50–70%) (Grunwald et al. 1999). In absence of the thyroid gland and with heightened levels of TSH (more than 30 IU/L), only some three-fourths of relapses and metastatic deposits of differentiated thyroid cancer have a manifest radioiodine uptake in WBS. (Alnafisi et al. 2000). This relatively low sensitivity depends on the introduced RP dose: the sensitivity of diagnostic WBS (up to 5 mCi) is below 60%, whereas that of post-therapy WBS (after introducing 100–200 mCi) reaches 75%. About 10–15% of metastatic foci visible in post-therapy WBS may be overlooked in diagnostic WBS scans (Fatourechhi et al. 2000). In cases of elevated TSH levels a WBS is done, and if it is positive, patients with differentiated thyroid cancer metastases undergo treatment with high doses of radioactive iodine.

The well-known diagnostic and therapeutic dilemma arises in cases of increase in TSH when diagnostic WBS results are negative. Patients with iodine-negative metastases usually do not receive treatment with high doses of radioactive iodine. Instead, if foci are localizable, they have to be surgically removed or corresponding anatomic regions have to be irradiated. This accounts for the need for alternative methods of localization of tumor affections. Conventional visualization modalities used for this purpose include ultrasonography, CT, MRI and osteoscintigraphy. At the same time, due to the low sensitivity of diagnostic WBS, a number of works have been published describing cases of empirical treatment with high doses of radioiodine in patients with negative diagnostic WBS and with high levels of TSH. Post-therapy WBS was implemented 7–12 days after administration of iodine. The diagnostic and therapeutic effect of this approach manifested itself with active uptake of iodine in the foci of lesion and with subsequent decrease in the level of TSH (Pineda et al. 1995; Van Tol et al. 2003). Such an approach is also efficient in patient with lung metastases (Pacini et al. 2001).

Clinical use of ^{18}F -FDG PET for localizing iodine-negative tumors has been demonstrated in a number of works in which sensitivity ranging from 71% to 94%

was observed (Frilling et al. 2001), positive prognostic value from 83% to 92% (Grunwald et al. 1999; Wang et al. 1999; Schluter et al. 2001; Welsch et al. 2007), specificity from 25% to 90% (Khan et al. 2003) and 93% negative prognostic value (Wang et al. 1999). However, the sensitivity of the method decreases with increase in positive tumor response to treatment and with reduction in size of the affected lymph nodes of the neck (Wang et al. 1999) and for miliary lung metastases (Chen et al. 2003; Hung et al. 2003). Follicular thyroid adenoma and sarcoidosis may influence the efficiency indices by inducing falsely positive results of ^{18}F -FDG PET (Grunwald et al. 1999).

The probability of a malignant thyroid disease is high in the case of focal uptake of ^{18}F -FDG in the projection of the thyroid gland in patients who had a PET procedure implemented for another disease (Van den Bruel et al. 2002). In most iodine-negative metastases an active uptake of ^{18}F -FDG is observed, which is accounted for by the low differentiation of cells having lost the capacity to absorb iodine but still secreting TSH and accumulating ^{18}F -FDG due to their intensive growth rate (Grunwald et al. 1999). High-dose radioiodine therapy has proved to be inefficient or poorly efficient as regards the suppression of viability of these iodine-negative but detected with ^{18}F -FDG PET metastatic lesions (Wang et al. 1999). And vice versa, in some patients with highly differentiated thyroid tumors capable of accumulating iodine in the foci of lesion, ^{18}F -FDG PET results may be falsely negative (Grunwald et al. 1999; Khan et al. 2003).

In a number of research works it has been observed that in patients with high levels of TSH and negative diagnostic WBS results, ^{18}F -FDG PET data conduce to a change in management tactics in more than half of cases (Wang et al. 1999; Goshen et al. 2003; Lind et al. 2003). Available accounts on the efficiency of ^{18}F -FDG PET in patients with high levels of TSH and negative post-therapy WBS are conflicting (Alnafisi et al. 2000; Van Tol et al. 2000). There has been also described coexistence of iodine-positive and ^{18}F -FDG-positive foci, especially in low-differentiated tumors. ^{18}F -FDG PET can be used in patients with known iodine-positive tumor foci in order to reveal parallel additional iodine-negative foci which are ^{18}F -FDG-positive (Grunwald et al. 1999). If iodine-negative foci exist simultaneously with iodine-positive ones, the success of further therapy with radioactive iodine is doubtful (Grunwald et al. 1999; Wang et al. 1999).

By ensuring PET and CT data coregistration in one procedure and permitting to draw correlation between functional and structural images, combined PET-CT scanners may improve localization of tumors (Zimmer et al. 2003), especially in early stages (Bockisch et al. 2003) and in interrelation with critical organs and structures (Larson and Robbins 2002).

There are other agents used for localizing metastatic lesions, including thallium-201- and technetium-99m-labeled tetrofosmin and isonitrile, which have a lower sensitivity and resolution compared with ^{18}F -FDG PET (Grunwald et al. 1999; Wang et al. 1999). Given that some metastases of differentiated thyroid cancer and most metastases of B-cell carcinoma express somatostatin receptors in high amounts, combined examinations with indium-111-labeled pentetreotide and ^{18}F -FDG PET for monitoring of tumor response to octreotide therapy are applied (Robbins et al.

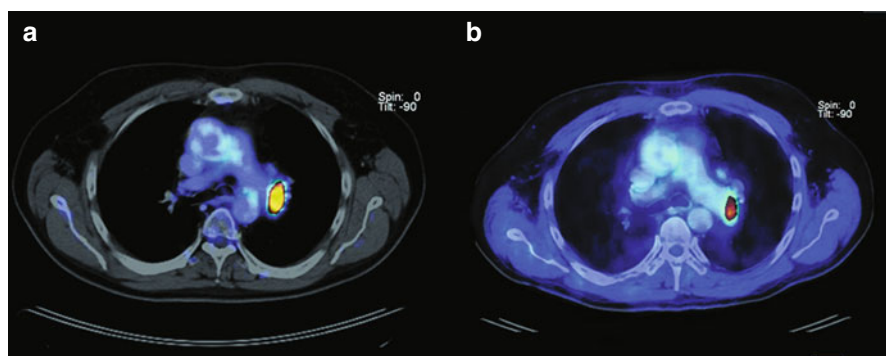


Fig. 3.3 (a–b) PET/CT with two RPs: ^{18}F -FDG and ^{18}F -DOPA. Medullary TC. Decrease in the level of calcitonin 4 months after the extirpation of the gland. Suspicion of relapse. PET/CT data indicate tumorous character of lesion of lymph nodes of the mediastinum (metastases) according to examinations with ^{18}F -FDG (a) and ^{18}F -DOPA (b)

2000). B-cell carcinoma is an exception among differentiated tumors, since it has unexpressed iodine avidity, whereas ^{18}F -FDG PET finds a disease undetectable by any other visualization method in 50% of cases (Lowe et al. 2003) with 92% sensitivity and 80% specificity (Plotkin et al. 2002). For medullary thyroid carcinoma, the sensitivity of ^{18}F -FDG PET is 76–78% and its specificity amounts to 79%, which exceeds by far the capacities of other methods (CT, MRI and SPECT with iodine-131-metaiodobenzylguanidine) in detecting primary foci and metastases, and at the same time is comparable in diagnostic information value with ^{18}F -DOPA (Fig. 3.3) (Diehl et al. 2001). Therefore, ^{18}F -FDG PET is an important method of localizing thyroid cancer relapses and metastases. Since the detection of TSH level and WBS occupy the first place in the diagnostic algorithm, for disease detection and localization respectively, the goal of ^{18}F -FDG PET presently consists in further search for a tumor focus in patients with negative WBS results and high TSH levels. PET has a very high positive prognostic value correlative with TSH levels. In examining patients with TSH levels <10, from 10 to 20 and >100 $\mu\text{g/L}$, ^{18}F -FDG PET provided true-positive results in 11%, 50% and 93% respectively (Schluter et al. 2001). According to specified data, it is better to implement ^{18}F -FDG PET after stimulation with recombinant TSH. The sensitivity of ^{18}F -FDG PET may be increased after an intramuscular injection of recombinant TSH (Petrich et al. 2001; Khan et al. 2003; Lind et al. 2003; Petrich et al. 2002; Van Tol et al. 2002) by way of enhancement of metabolic activity of thyroid tissue similar to TSH secretion stimulation and radioiodine uptake carried out with the help of recombinant human TSH (Petrich et al. 2001; Khan et al. 2003; Lind et al. 2003; Petrich et al. 2002; Van Tol et al. 2002). A number of research works have shown that PET sensitivity is higher if diagnostic WBS is negative, which confirms the theory of progressive dedifferentiation of thyroid tumors with loss of capacity to uptake iodine and with acceleration of the rate of glucolysis. However most of the available data are based on research done after

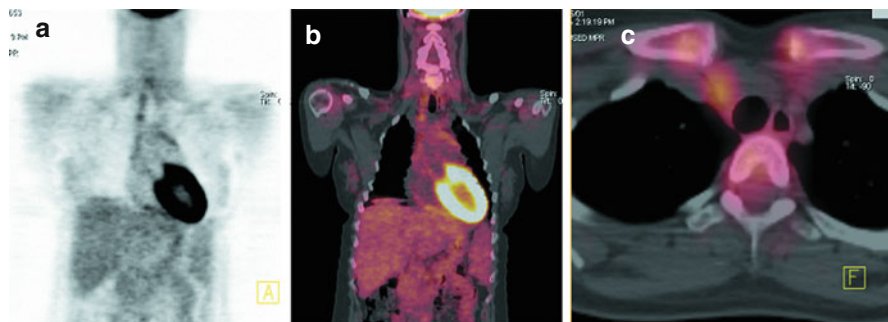


Fig. 3.4 (a–c) ^{18}F -FDG PET/CT in differentiated thyroid cancer. Total strumectomy in past history, rise in the level of thyroglobulin and soft-tissue formation in the anterior mediastinum according to ultrasound data. Suspicion of relapse of the neoplasm. ^{131}I diagnostic WBS provided negative results. In the fused ^{18}F -FDG PET/CT image (b, c), a focus of hypermetabolism of glucose anterior and to the right from the aortic arch is revealed coinciding with the volumetric formation detected by CT

negative diagnostic WBS. As for data obtained after negative post-therapy WBS, they are few and controversial (Fig. 3.4).

Possible coexistence of iodine-positive and iodine-negative lesions and lack of correspondence in localization of iodine-positive and ^{18}F -FDG-positive foci are the two clinical problems that can give impetus to further increase of the role of FDG PET even in the presence of an iodine-positive disease. Administering high radioiodine doses has proved to be inefficient or little efficient in treating ^{18}F -FDG-positive metastatic lesions (Wang et al. 2001) which most probably represent low-differentiated tumors. PET examinations of differentiated thyroid cancer patients became possible with appearance of positron-emitting iodine-124 in the arsenal of physicians (Fig. 3.5). Lower sensitivity of other tumor-seeking agents, including thallium-201, $^{99\text{m}}\text{Tc}$ -tetrofosmin and $^{99\text{m}}\text{Tc}$ -isonitritil may be in part accounted for by lower resolving capacity of SPECT visualization compared with PET and by difference in mechanisms of RP uptake. If it is necessary to differentiate enlarged lymph nodes because of inflammatory alterations due to their metastatic lesion, $^{99\text{m}}\text{Tc}$ -isonitritil is the agent of choice. However, sensitivity of SPECT with $^{99\text{m}}\text{Tc}$ -isonitritil is lower than that of ^{18}F -FDG PET in examination of residual lesion of lymph nodes of the neck and in miliary metastases to lungs (Chen et al. 2003).

Although anatomic visualization methods including US, MRI and CT are often used in case of negative diagnostic WBS results, their lower specificity, especially in patients with altered anatomy, limits the amount of obtainable information. ^{18}F -FDG PET also provides prognostic information (Macapinlac 2001; Wang et al. 2000). The bigger the general number of ^{18}F -FDG uptake foci, the lower is survivability.

Using PET during a 2-month treatment period helps detect patients reacting positively to isotretinoin treatment and those for whom it is inefficient (Petrich et al. 2002).

So, TSH level detection in blood serum and diagnostic WBS proved to be rather efficient methods of control of remission and visualization of relapses during the post-therapy period of observation. In cases of negative results of diagnostic WBS,

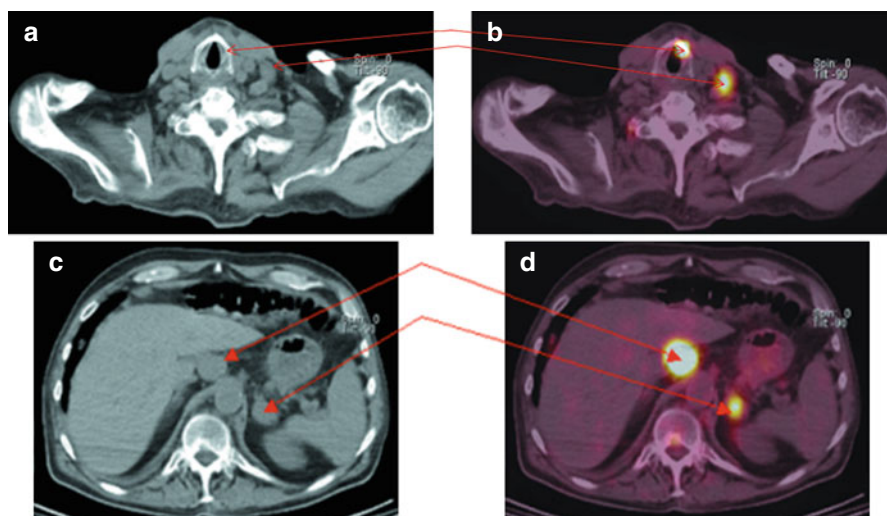


Fig. 3.5 (a–d) ^{124}I -PET/CT of Thyroid cancer, regional and spread lymph node metastases (a, c) CT data. (b, d) Fused ^{124}I -PET/CT. Foci of pathological uptake in the thyroid gland with infiltration of thyroid cartilage, in a cervical lymph node, coelical and close to esophagus are detected (arrows). This approach enables to stage the disease, assess operability and possibility of radioiodine therapy and to make dosimetric calculation

but with high TSH levels, ^{18}F -FDG PET with its superior sensitivity and higher specificity compared with other functional and anatomic visualization methods is the method of choice for detecting relapses and metastases. The same can be said as regards combined PET-CT both with FDG and with iodine-124, a newly developed method of localization of tumor lesion in thyroid cancer (Freudenber [2004](#) and Palmedo [2006](#)).

Suggested Reading

Boerner AR, Petrich T, Weckesser E et al (2002) Monitoring isotretinoin therapy in thyroid cancer using ^{18}F -FDG-PET. *Eur J Nucl Med Mol Imaging* 29:231–236

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Currently breast cancer (BC) is the most frequent of all oncological diseases, both in incidence and in mortality. Suffice it to say that annually more than one million cases of BC are registered in the world. In the USA this disease is detected in roughly 180,000 women per year. In Russia, BC incidence is continually growing. In 1980 it constituted 22.6 per 100,000 of the population, while in 2003 it was already 42.8. The peak of BC incidence falls on the age of 55–59 years (138.9 per 100,000 of the population) and 60–69 years (145.2 per 100,000 of the population) (Semiglazov et al. 2001).

The classification of breast cancer follows the TNM scoring.

4.1 Diagnosis of Breast Cancer

Self-examination (visual examination and palpation) of the mammary glands, according to WHO recommendations should be done once a month during the first days after menstruation, starting from the age of 25 years.

Physical examination of the mammary gland done by an oncologist is of much importance in diagnosing breast cancer. During the examination, symmetry of location and form of the breast glands, the state of the skin and nipples etc. are assessed. Besides superficial and deep palpation of the breast glands, axillary, subclavicular and cervico-supraclavicular lymph nodes are done. The diagnostic accuracy of this method is largely determined by the specialist's professional skill, but on the whole it does not exceed 45–60% for primary tumor and 50–70% for metastases to regional lymph nodes (Portnoi et al. 1995).

Currently, the main instrumental method of radiological examination of BC patients is still X-ray mammography. The improvement of X-ray mammography apparatuses has permitted a decrease of radiation exposure to 0.002–0.003 Gy, and in modern low-dose X-RAY MAMMOGRAPHY the effective dose falling on the breast gland has decreased to 0.0002–0.0003 Gy. The analysis of some examination results has showed that use of X-ray mammography as screening method of diagnosing BC leads to decrease in mortality by no less than 30% (Semiglazov et al. 2001).

X-ray mammography sensitivity according to different authors varies from 70% to 92%. At the same time, minimum forms of BC are detected in 76.5% of cases. However, the relatively low specificity of the method remains the main limiting factor of its use. Suffice it to say that in roughly 30% of cases when mammography diagnoses BC, the results of postoperational biopsy attest to the benign nature of the lesion (Tsyb and Tlepshukov 1989; Nystrom et al. 1993; Kharchenko et al. 1996, 1999; Kholin 1996).

Currently, ultrasound (US) is widely used for diagnosing BC; along with X-ray mammography, it can be considered as the main method of screening diagnosis of BC. In particular, ultrasound mammography takes the leading part in differentially diagnosing between solid and cystic masses. The disadvantages of USD include the impossibility of visualizing microfoci of malignization in the presence of diffuse proliferative fibroadenomatosis in the patient. Some authors think that US does not have any independent significance in diagnosing BC since it is characterized by a relatively low sensitivity and may be used only for differential diagnosis of cysts and solid masses and in women younger than 30 years, and for pregnant and nursing women in case of detection of a palpable mass (Basset and Kimme-Smith 1991; Harvey et al. 2008). According to some authors (Zaitsev et al. 1996, 1997), mammography should be used as the first stage of examination in elderly women in case nonpalpable masses are detected, in the presence of tumor focus localized behind the nipple. The authors recommend implementing US mammography in young women, in case of distinctly palpable masses as well as in cases when tumor focus is localized in areas of the breast gland inaccessible to X-ray mammography.

CT is an efficient additional method of diagnosis, permitting significant additional information to be obtained in case of the infiltrative-edematous form of breast cancer, tumor relapses and neoplasms localized in the retromammary space. This method is particularly valuable in the presence of metastases to lymph nodes of axillary and subclavicular areas (Taira et al. 2008).

MRI has a high efficacy when used in the dynamic regime with contrast. This method, when used without paramagnetic contrast agents, is less informative than mammography. According to different authors, the sensitivity of dynamic contrast-enhanced MRI (DCMRI) in diagnosing breast cancer reaches 95–98%, but its specificity remains relatively low (50–80%) and depends to a large extent on the state of surrounding glandular tissue (Belenkov et al. 1996; Arzumanova et al. 1999; Bedrosian et al. 2000; Dewey and Martus 2008). The tangible advantage of DCMRI over X-ray mammography and US is its ability to detect within one examination metastatic lesion of lymph nodes of the retromammary space and anterior mediastinum. In consequence, this method of radiologic examination may be used for assessing the dissemination of the tumor process.

Recently, the question of using radionuclide methods of visualization in diagnosing BC has been widely discussed. ^{99m}Tc -technetyle scintigraphy is a highly informative method of diagnosis in detecting primary focus and regional metastases. The exact mechanism of ^{99m}Tc -technetyle uptake by tumor cells is not clear for now. It is known that about 90% of this radiopharmaceutical (RP) accumulates in the

mitochondria of tumor cells. At the same time, other research has shown that ^{99m}Tc -technetyle uptake depends to a larger extent on the activity of cell proliferation than on the density of mitochondria and processes of neovascularization. The sensitivity, specificity and diagnostic accuracy of the method in detecting palpable malignant breast neoplasms according to some authors make up 84%, 80% and 82% respectively (Khalkhali and Vargas 2001; Liang et al. 2008). It should be noted that the method of two-stage scintimammography done in the regime of double scanning (10–20 min and 2 h after the introduction of RP) permits detection not only of the primary focus and metastatic lesions of lymph nodes but also the resistance of the primary focus and regional metastases to chemotherapy since ^{99m}Tc -technetyle and tetrophosmin used in this method are substrates of *MDR-1* gene-encoded P-glycoprotein, ensuring active transport of xenobiotics from cells.

SPECT is also rather widely used in clinical practice, along with planar scintigraphy, and has some advantages over the latter. For example, Nagaraj et al. (1994) detected on the material of 34 BC patients significant information from ^{99m}Tc -technetyle SPECT in confronting the data with those of a planar examination done with the same RP. With roughly the same values of sensitivity, SPECT was characterized by a much higher specificity in diagnosing primary tumor node compared with planar scintimammography (70% and 50% respectively). The specificity of the SPECT examination in detecting metastatic lesions of axillary lymph nodes was also higher than that of planar scintimammography (100% and 70% respectively). However, it should be noted that the resolving capacity of modern gamma-cameras does not exceed 1 cm. This restricts the suitability of using scintimammography (both planar and SPECT) in the presence of a primary tumor focus and deposits in lymph nodes with diameter less than 1 cm.

Diagnosis of metastases to regional lymph nodes is still a weak link in assessing generalization of breast cancer. Direct lymphangiography used for assessing regional lymphatic metastasis has not received wide use because of its invasivity and danger of complications. Nuclide lymphoscintigraphy with technetium-based RP is a more available and less dangerous method, but like direct lymphoscintigraphy it does not allow differential diagnosis between hyperplasia, inflammatory lymphadenitis and metastatic lesion of lymph nodes (Palmedo et al. 1996; Ryannel et al. 1998).

4.2 PET in Diagnosis of Breast Cancer

4.2.1 Diagnosis of Primary Tumor Focus

Breast cancer is characterized by high glycolytic activity, which results in intensive ^{18}F -FDG uptake in tumor tissue. The level of glycolysis, and consequently that of ^{18}F -FDG hyperfixation, depends on the histological type of primary tumor focus.

In 1989, Kubota et al. (1989) described focal RP uptake in a BC patient. A pilot study done by Wahl et al. (1991) in 12 patients with histologically confirmed BC revealed the high informative value of ^{18}F -FDG PET. The size of tumor in all the examined patients exceeded 3 cm. Later examinations done in a big patient group

Table 4.1 Sensitivity, specificity and diagnostic accuracy of ^{18}F -FDG PET in diagnosis of the primary tumor in BC patients according to various authors

Author	Year	Patient number	Sensitivity (%)	Specificity (%)	Accuracy (%)
Zhao et al.	2007	24	92.7	90.1	91.4
Mavi et al.	2006	152	94.1	89.3	90.2
Tyutin et al.	2003	78	97.1	100	97.8
Scheidhauer et al.	2001	117	93.0	75.0	89.0
Rostom et al.	1999	93	91.0	83.0	89.0
Noh et al.	1998	27	96.0	100	97.0

(124 patients) confirmed that ^{18}F -FDG PET is a highly informative method of detecting primary tumor focus in BC (Phelps 2004). The sensitivity of the method made up 92% and its specificity was 92%. The size of tumor was smaller than 3 cm in 79 patients. Summary data on the informative value of ^{18}F -FDG PET in detecting primary tumor focus in BC patients are displayed in Table 4.1.

For example, Schirrmeister et al. (2001) have detected that in case of infiltrating ductal carcinoma a higher RP uptake by tumor cells is observed than in lobular tumor. Besides, direct correlation between ^{18}F -FDG uptake [in particular, the standardized uptake value (SUV)] and the degree of tumor malignancy has been observed. In most cases, primary tumor is defined as the focus of high RP uptake (Fig. 4.1). SUV values in tumor tissue and T/NT ratio significantly vary, however, according to our data, maximum SUV (SUVmax) averages 3.71 ± 0.21 and T/NT ratio 7.08 ± 0.99 (Granov 2007).

Currently much attention is given in literature to correlation between ^{18}F -FDG uptake by BC cells and the level of expression of the p53 gene. This gene governs the transcription of at least two sets of genes. One of the set is responsible for a temporary stop in cytokinesis in the phase G1 and the other controls apoptosis initiation. Besides, the non-mutant gene p53 suppresses expression of genes responsible for synthesis of the receptors GLUT1 and GLUT4, whose number determines ^{18}F -FDG uptake by tumor cells. According to some authors, there is a strong direct correlation between the level of uptake of the mutated protein p53 (in consequence of mutation of the corresponding gene) in breast tissue and the level of ^{18}F -FDG hyperfixation in the area of primary tumor focus (Hiraki et al. 1988; Utech et al. 1996; Crippa et al. 1998; Rostom et al. 1999).

A number of works are devoted to comparison of the diagnostic accuracy of ^{18}F -FDG PET with that of other methods of radiologic visualization. For example, according to Bassa et al. (1996) the sensitivities of ^{18}F -FDG PET, mammography and USD were, respectively, 100%, 62.5% and 87.5%. The size of primary tumor focus ranged from 1.7 to 9.0 cm. According to Tyutin et al. (2001), the sensitivity, specificity and diagnostic value of ^{18}F -FDG PET in detecting primary tumor in BC patients was 96.8%, 100% and 97.2% respectively. In this work, the sensitivity of ^{18}F -FDG PET was higher for the group of patients with palpable BC masses (Fig. 4.2).

At the same time, no significant difference in efficacy of the method was observed depending on concomitant fibroadenomatosis (Fig. 4.3). The accuracy of X-ray

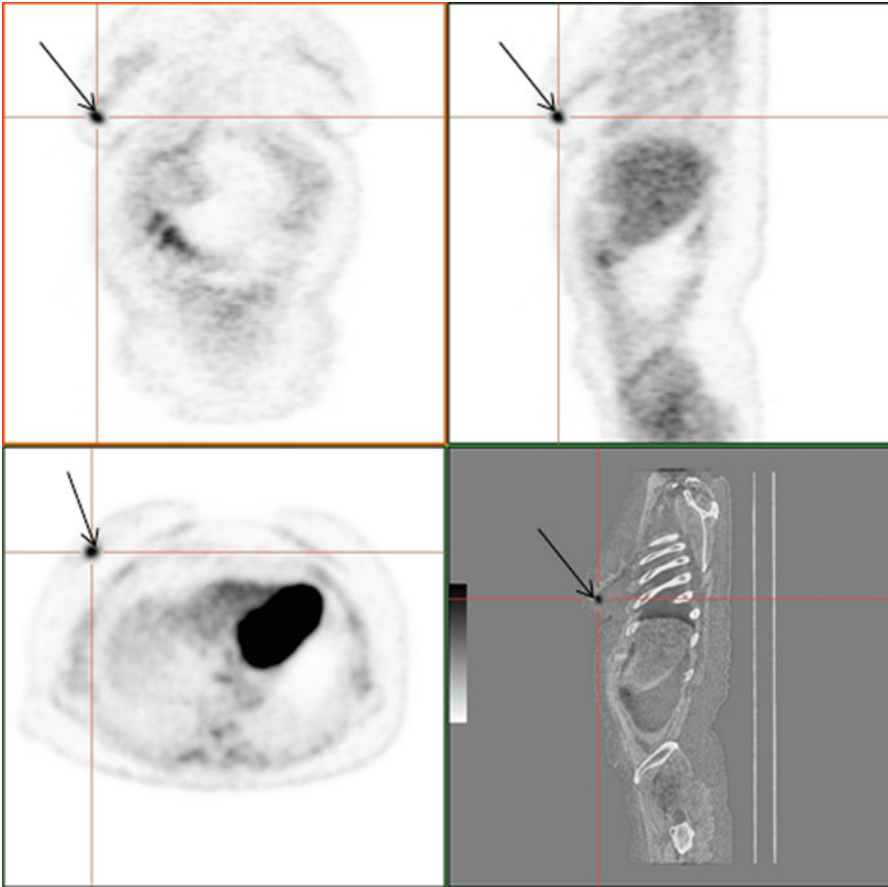


Fig. 4.1 Patient, 35 years old. Breast cancer T3N0M0. ^{18}F -FDG PET / CT: Pathological uptake in the external quadrant of right breast (*arrows*)

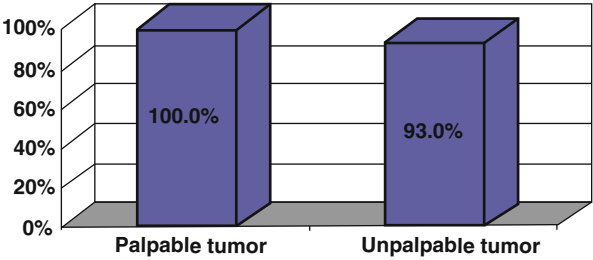
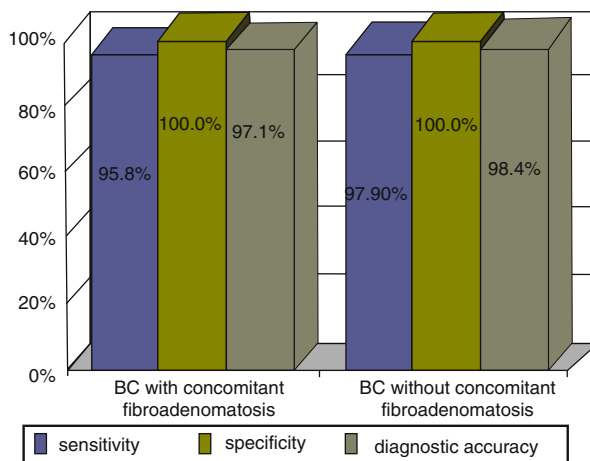


Fig. 4.2 Sensitivity of PET with ^{18}F -FDG depending on size of a primary tumor focus

Fig. 4.3 Informativity of PET with ^{18}F -FDG in diagnosis of BC depending on the presence of concomitant fibroadenomatosis



mammography, US and DCMRI in this work was significantly lower compared with that of ^{18}F -FDG PET and was defined as 87.3%, 90.1% and 90.3% respectively.

False-negative cases in ^{18}F -FDG PET are usually conditioned by small size of the formation (less than 0.5 cm). Also, Paget's cancer (tumor of the nipple and breast areola) is characterized by low metabolic activity of glucose and may also be a cause of false-negative results. False-positive data may be obtained in patients after biopsy and are usually conditioned by an inflammation area in this site. Implementing a delayed scan (120–240 min after RP introduction) allows high accuracy in differentially diagnosing between tumor tissue and inflammatory changes. Noh et al. (1998) revealed that in BC an increase in SUV in tumor (at least by 10%) was observed. At the same time this index does not significantly change in inflammatory areas after the repeated scan or its further decrease is observed. Similar data were obtained by Boerner et al. (1999) who examined 29 BC patients. Data collection was done 1.5 and 3 h after RP introduction. A significant increase in the tumor/background ratio was observed during the second scan (from 1.2 ± 0.6 to 6.1 ± 3.0). Tumor detectability according to the authors increased from 83% to 93%.

In some studies, the patient's position during scanning (on their back or on their stomach) influences the efficacy of the method. SUV and T/NT ratio values in most cases were higher when examining patients lying on their stomachs. However, these data had no impact on the sensitivity, specificity and diagnostic accuracy of PET (Greco et al. 2001).

So it is clear that PET is an efficient additional method of diagnosing primary tumor focus in BC. However, its use is justified only in difficult diagnostic situations. Examining patients suspected of BC should always begin with physical examination (palpation) of the breast glands and regional lymph nodes (axillary and subclavicular). If pathologic changes are detected, recourse is made to X-ray mammography and USD as well as to USD-controlled puncture biopsy. In difficult

clinical situations as well as for the purpose of detecting metastases to internal lymph nodes, it is suitable to use DCMRI, whose results may be completed by data from ^{99m}Tc -technetium scintimammography. If after this examination there remain doubts as to the malignancy of the pathologic process, ^{18}F -FDG PET should be implemented. Trepan biopsy is done at any stage of diagnostic search if signs of malignant neoplasm are discovered.

4.2.2 Diagnosis of Regional Metastases

One of the first studies devoted capacities of PET in diagnosing regional metastases in BC patients was that of Tse et al. (1992). The state of lymph nodes according to PET results was correctly assessed in 11 out of 14 patients examined. Further research done on a large clinical scale attested to the high efficacy of the method in detecting regional metastases of BC. The sensitivity of the method in diagnosing metastatic lesions of axillary, subclavicular and parasternal lymph nodes ranges within 85–95%, its specificity varies from 66% to 100% and its diagnostic value ranges from 74% to 94%. In addition, PET is more informative in detecting axillary and subclavicular lymph nodes compared with other methods of radiologic visualization. In the research done by Adler et al. (1997) on 54 patients with lesions of regional lymph nodes, the diagnostic accuracy of PET, USD and ^{99m}Tc -technetium scintimammography were defined as 94.0%, 84.9% and 83.2% respectively. It is important to note that the efficacy of ^{18}F -FDG PET in detecting regional metastases is comparable with that of biopsy of sentinel lymph nodes. Data of different authors on the efficacy of ^{18}F -FDG PET in diagnosing metastatic lesion of axillary lymph nodes are presented in the Table 4.2.

As is clear from Table 4.2, most studies show high sensitivity of the method in detecting regional metastases in BC patients. Usually, lesion foci are characterized by high RP uptake with SUVmax averaging 2.5 ± 1.12 (Fig. 4.4) False-negative results are usually conditioned by small (less than 0.5 cm) size of lesion focus (including cases of micrometastases). Sometimes diffuse uneven RP uptake in apparent brown adipose tissue and along the muscles of the neck due to their hyper-tonus makes it difficult to visualize the cervical group of lymph nodes. Using PET/CT fused images the misinterpretation of cervical tracer uptake decreases because of better differentiation between brown fat tissue and FDG-positive lymph nodes (Rousseau 2006 and Paidisetty 2009). Additionally, false-negative conclusions may be due to the patients' obesity, which has a negative impact on the quality of images. Data on the specificity of the method are more ambiguous. For example, according to some data the specificity of ^{18}F -FDG PET in diagnosing axillary, subclavicular and retrosternal lymph nodes reaches 100%. False-positive results in detecting metastatic lesions of lymph nodes of the axillary and subclavicular groups have not been observed (Granov 2007).

Similar data are presented in the comparative study of Kubota et al. (1989). According to them, the specificity of ^{18}F -FDG PET also made up 100% and significantly exceeded that of USD (50%). However, some authors' results suggest

Table 4.2 Sensitivity, specificity and diagnostic accuracy of ¹⁸F-FDG PET in diagnosis of the regional metastases in BC patients according to various authors

Author	Year	Patient number	Sensitivity (%)	Specificity (%)	Accuracy (%)
Granov et al.	2007	83	90.7	100	94.0
Zhao et al.	2007	24	93.4	89.1	92.5
Kumar et al.	2006	49	89.5	84.4	
Greco et al.	2001	167	94.0	86.0	90.0
Rostom et al.	1999	74	86.0	100	90.0
Noh et al.	1998	24	100.0	92.0	96.0
Crippa et al.	1997	72	85.0	91.0	89.0
Utech et al.	1996	124	100.0	75.0	88.0

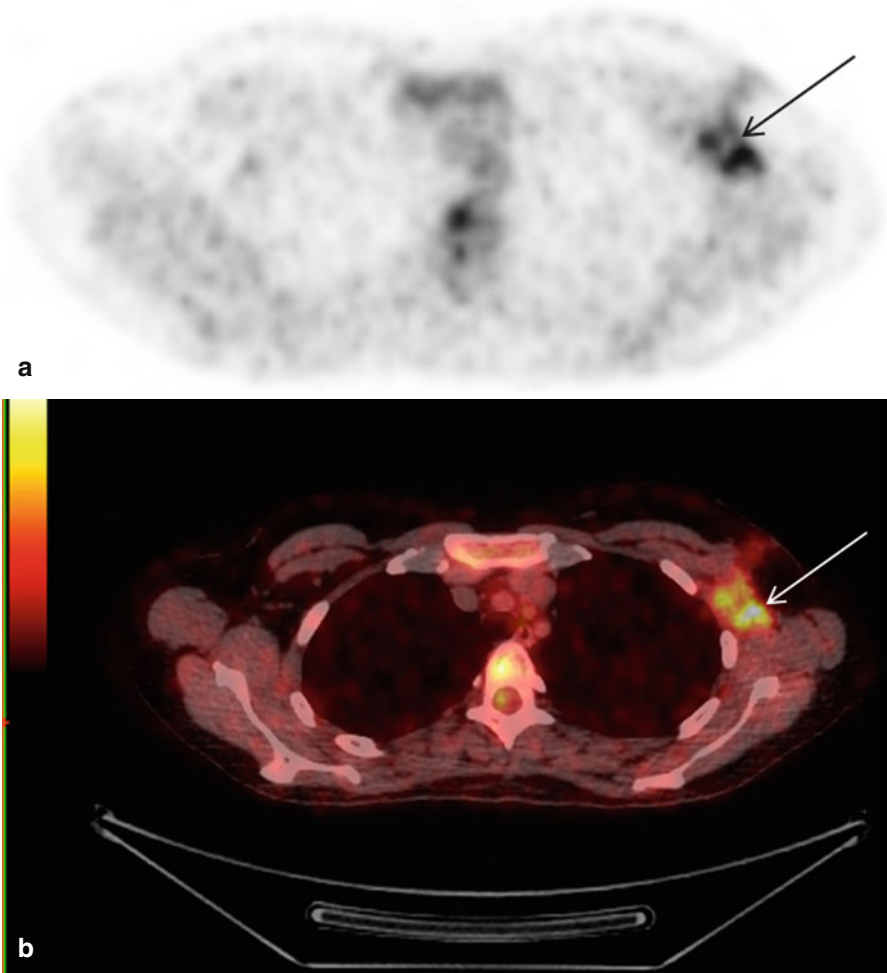


Fig. 4.4 (a, b) Breast cancer, T2N1M0. In ¹⁸F-FDG PET (a) and PET/CT (b) pathological uptake (SUV = 5, 4) is detected in left axillar lymphatic nodes (*arrow*)

a relatively low specificity of the method in detecting axillary and subclavicular lymph nodes. For example, a prospective examination of 124 BC patients has shown that PET specificity in detecting affected lymph nodes made up 75%. False-positive results are then associated with ^{18}F -FDG uptake in areas of reactive inflammation, sinus histiocytosis, and moderate plasmacytosis and in macrophages loaded with hemosiderin (Ohta et al. 2000).

4.2.3 Diagnosis of Distant Metastases

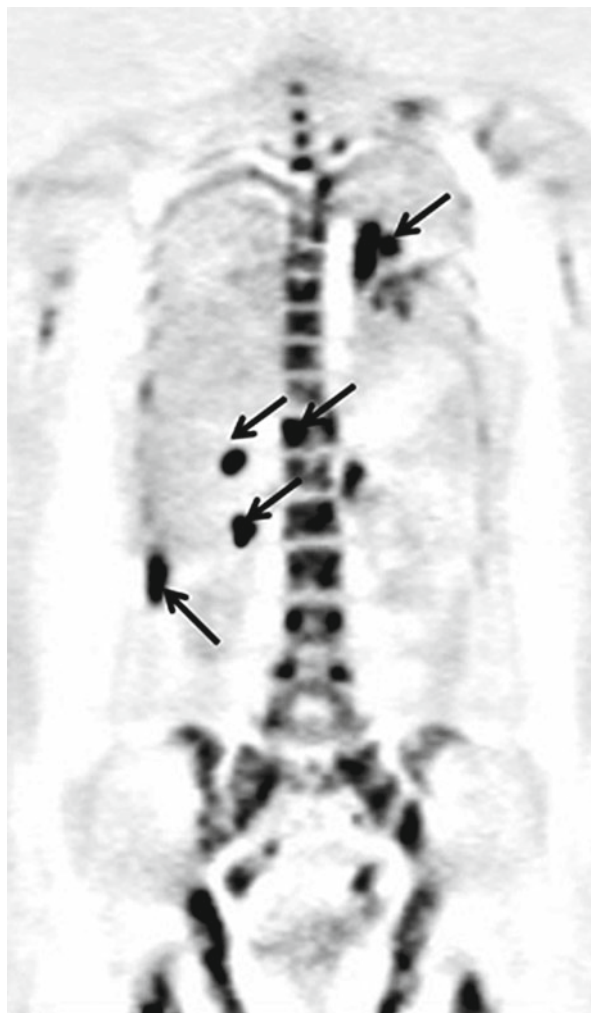
As is known, the accuracy of BC staging permits the optimization of patient management. Most authors' results indicate that whole-body ^{18}F -FDG PET makes it possible to obtain reliable information on the dissemination of BC within one scan (Fig. 4.5). Pilot research by Wahl et al. (1991) showed that ^{18}F -FDG PET permits the detection of metastatic lesions of the bones and soft tissues in patients with late stages of BC. In later reports, the efficacies of ^{18}F -FDG PET and other methods of visualization were compared. According to some data, PET sensitivity in detecting metastatic lesion of the skeleton made up 90% (Granov et al. 2007). The same index was defined as 50% for $^{99\text{m}}\text{Tc}$ -technetyle osteoscintigraphy. Similar data were reported by Foxcroft et al. (2000) in metaanalysis over studies done over 11 years, where ^{18}F -FDG PET results were compared with those of osteoscintigraphy. The total sensitivity of PET in detecting metastases to the bones made up 81% and its specificity was 93%. The same indices for scintigraphy of the skeleton were 78% and 79% respectively. In some studies it has been found out that the efficacy of ^{18}F -FDG PET in detecting osteoblastic metastases of BC is inferior to that of osteoscintigraphy. However, the diagnostic accuracy of PET in detecting osteolytic lesions is significantly superior. This is due to the difference between mechanisms of uptake of osteotropic RP used in scintigraphy and ^{18}F -FDG. $^{99\text{m}}\text{Tc}$ -phosphonates are known to become bound with the mineral component of bone tissue and their uptake is conditioned first of all by the level of osteoblastic activity as well as by the magnitude of blood flow. Thus, RP hyperfixation in osteoscintigraphy reflects only the osteoblastic reaction to destruction of bone tissue by tumor cells.

At the same time, ^{18}F -FDG uptake correlates only with the degree of metabolism of tumor tissue. Since PET and skeleton scintigraphy permit the assessment of different mechanisms of metastasis formation in the bones and complement each other, most authors recommend implementing both of these examinations for assessing the dissemination of metastatic lesions of bone tissue.

In the diagnosis of metastatic lesions of the lungs and liver, ^{18}F -FDG PET is on the whole inferior in informative value to modern structural methods of radiologic examination (MDCT and MRI), which have a higher resolving capacity. However, PET data may have a decisive role in differentially diagnosing and assessing the character of detected lesion foci, especially as regards solitary masses.

Yap et al. (2002) studied the impact of ^{18}F -FDG PET results on BC staging. It has been established that PET data permitted the restaging of the disease in 36% of

Fig. 4.5 Breast cancer, T3N1M1. According to the ^{18}F -FDG PET data, a multiple metastatic lesion of lungs, liver and bones is noted



cases. A higher stage of the disease was observed in 28% of patients, a lower stage was revealed in 8% and therapeutic management was corrected in 40% of patients on the base of PET data.

As is clear from the presented data, whole-body ^{18}F -FDG PET permits reliable information to be obtained on the dissemination of BC within one examination.

4.2.4 Evaluation of Efficiency of BC Treatment

^{18}F -FDG PET plays a major role in interpreting the results of radiological, surgical and chemical therapies for BC, particularly in difficult clinical situations in cases of

high levels of tumor markers and in cases of difficulty in differentially diagnosing between cicatrical tissue and continued growth, post-radiation necrosis and relapse. An important advantage of ^{18}F -FDG PET over other methods of visualization (mammography, USD, DCMRI) is its ability to detect changes in tumor focus and regional metastases at earlier stages directly during polychemotherapy and (or) radiological therapy.

One of the first studies devoted to treatment efficiency evaluation in BC patients by means of PET was done by Minn et al. (1989). Later, Wahl et al. (1991) discovered that in the absence of changes in size of primary tumor in BC patients according to X-ray mammography and US data, PET permitted the determination of complete or partial metabolic response to treatment after three courses of polychemical and hormonal therapies, confirmed by histological examinations. RP uptake in the area of the primary tumor focus in these patients decreased on average by 78% by the 8th day after the start of treatment. ^{18}F -FDG and ^{11}C -methionine PET were included in this study. A metabolic response was obtained 1–2 weeks after the beginning of polychemotherapy. Interesting data have been obtained in the PET center of the RSCRST: ^{18}F -FDG PET was performed twice – before the onset of treatment and after four courses of non-adjuvant polychemotherapy. Further, morphological examination was done twice: that of trepan biopsy material before treatment and that of surgically removed affected tissues after the end of therapy. Depending on the results of histological study of the surgical specimen, all the patients were divided into three groups. The first group consisted of patients in whom tumor cells were absent in histological analysis of the surgical specimen. The second group included persons in whom tumor cells were detected during histological analysis but a decrease (in different degrees) in their number was observed compared with the data of trepan biopsy done before treatment. The third group was composed of patients in whom the number of tumor cells in the area of primary tumor focus did not change compared with the results of the histological study done before the beginning of the course of non-adjuvant polychemotherapy. After four courses of non-adjuvant polychemotherapy in all the patients of the first group, according to ^{18}F -FDG PET performed after surgical treatment absence of RP uptake in the projection of tumor focus was established, which indicated complete suppression of tumor metabolic activity (Fig. 4.6). In the patients of the second group, a decrease in size of tumor focus and reduction of glucose uptake in its projection (in different degrees) were observed during PET, which was considered as partial regression of tumor (Fig. 4.7). In the patients of the third group, ^{18}F -FDG PET data in all the cases indicated absence of changes in primary tumor focus or its increase in size. In all the patients of this group, PET data were in direct correlation with the results of histological analysis of the surgical specimen.

Dehadashti et al. (1998) assessed tumor metabolic response in treatment with tamoxifen. ^{18}F -FDG and ^{18}F -estradiol PET was implemented in women with histologically proved estrogen positive breast cancer in the post-menopausal period. The ability of PET to predict tumor response to treatment was assessed in the study. All the patients in whom positive dynamics was later observed during treatment, initially had higher ^{18}F -FDG and ^{18}F -estradiol uptake in the area of lesion. Consequently the

Fig. 4.6 (a–f) Infiltrating ductal carcinoma (by trepanobiopsy data, e). Comparison of results of PET with ^{18}F -FDG (a) and MRI with contrast enhancement (b) in a patient with BC before the treatment and after neoadjuvant polychemotherapy. According to the PET data, after the treatment (d) there is a notable absence of the RP uptake. According to the MRI data (c), there are notable positive dynamics, but a small area of pathologic contrast enhancement is preserved. Histological investigation of the surgical specimen (f) obtained after neoadjuvant polychemotherapy revealed no tumor cells in the tissue

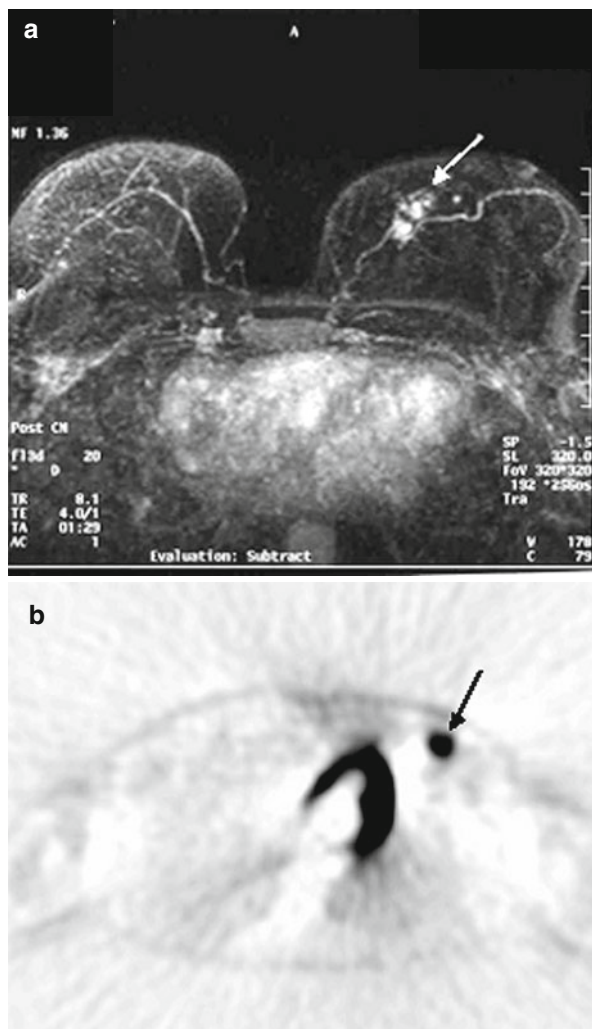


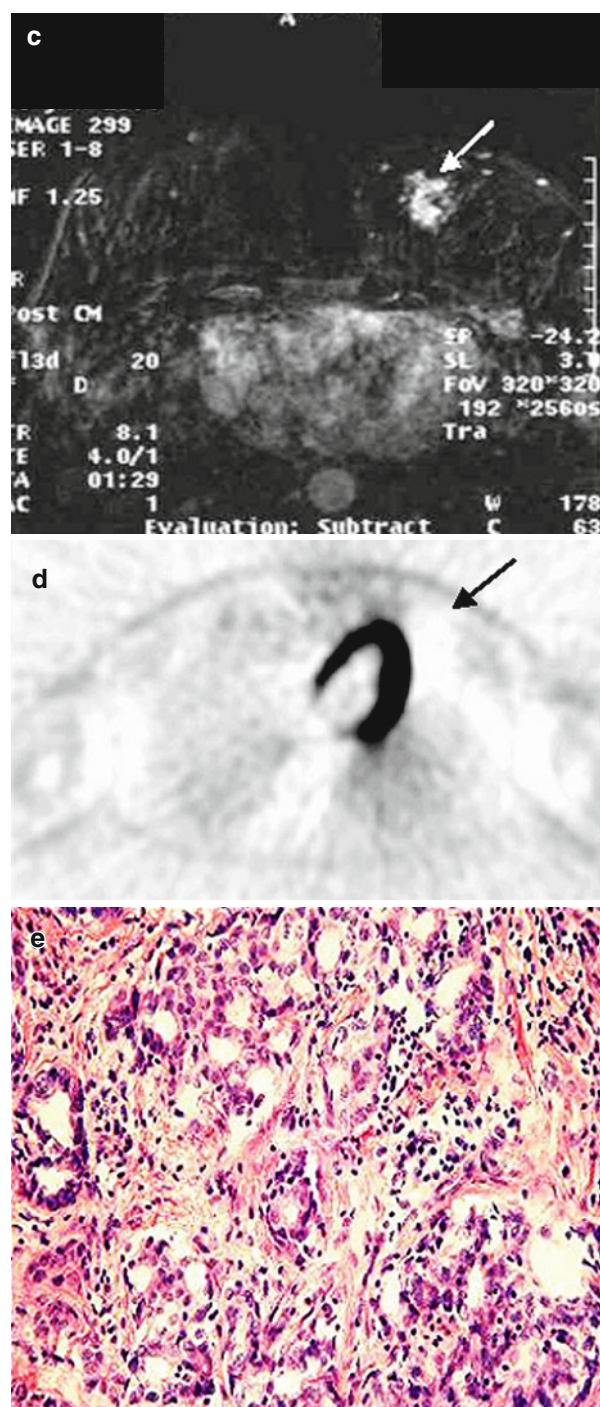
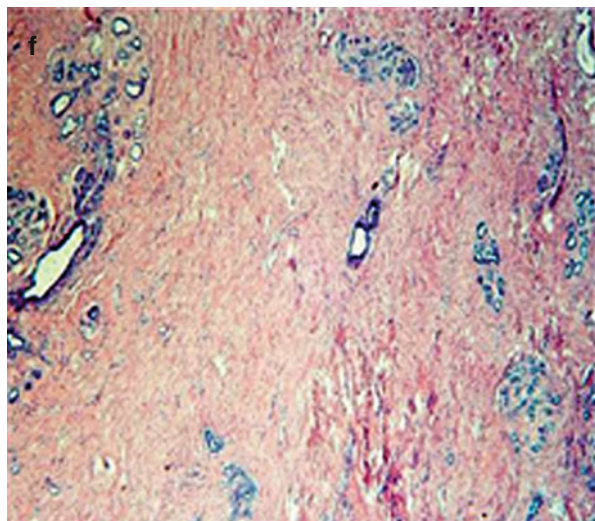
Fig. 4.6 (continued)

Fig. 4.6 (continued)

level of RP hyperfixation in primary tumor focus may be a predictor of estrogen-depending breast cancer response to treatment.

Research of Schelling et al. (2000) also showed high diagnostic value of ^{18}F -FDG PET in assessing the efficiency of BC treatment. Tumor response to poly-chemotherapy was assessed in this work. Receiver operator characteristic (ROC) analysis permitted the discovery of the optimum predictive diagnostic accuracy of PET in the presence of an SUV decrease of 55% after treatment. In other words, an SUV decrease during treatment of more than 55% compared with initial examination permits the prediction of a high efficiency of treatment with maximum accuracy. After the first course of therapy when the indicated threshold value of SUV decrease was used, the predictive accuracy of ^{18}F -FDG PET was 88%, while after the second course it was 91%. In another study, PET was performed in BC patients with metastatic lesion of axillary lymph nodes. The sensitivity of the method in assessing treatment efficiency was 90% and its specificity was 74%. In this study, an 20% SUV decrease during treatment was used as a criterion of exclusion in statistic data processing (ROC analysis) (Phelps 2004).

The reported data indicate that ^{18}F -FDG PET not only permits assessment of the dissemination of tumor but also evaluation with high accuracy of the efficiency of treating BC.

The dynamics of SUV or T/NT ratio during treatment reflects the activity of metabolic changes in tumor focus at early stages of therapy when other methods of radiological visualization (X-ray mammography, US, MRI) do not register significant changes in size of the tumor focus. Most researchers observe direct correlation between ^{18}F -FDG PET data and results of analysis of tissue specimens in BC patients. In this context we can draw the conclusion that SUV and T/NT ratio are in

Fig. 4.7 Infiltrating ductal carcinoma (by trepanobiopsy data, **a**). Results of PET with ^{18}F -FDG before (**b**) and after (**c**) neoadjuvant polychemotherapy. According to the PET data after the treatment (**d**), a decrease of the RP uptake was observed in the area of a primary focus (partial metabolic response). After polychemotherapy (operative samples, **d**), a decrease in the number of tumor cells is observed

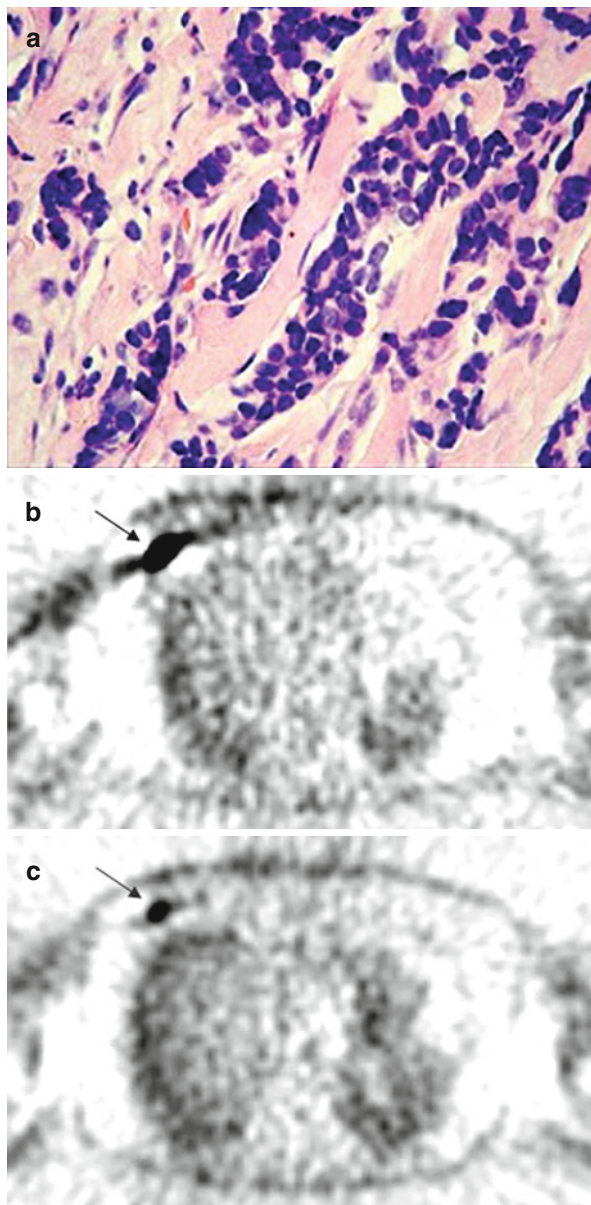
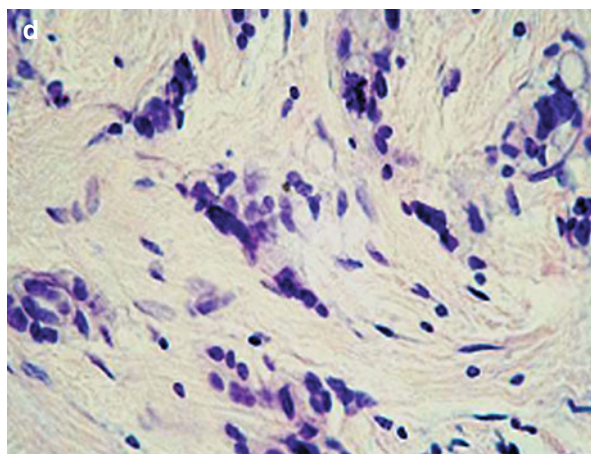


Fig. 4.7 (continued)

direct correlation with the amount of viable malignant cells in tumor stroma as well as with their proliferative activity (Phelps 2004; Granov et al. 2007).

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Timely diagnosis of lung cancer (LC) is difficult in the stage in which radical treatment is possible, due to scarce clinical manifestations. Numerous symptoms usually appear only as the tumor progresses (Zyryanov et al. 1997). Clinical manifestations of LC depend on three main factors: clinical-anatomic form of the disease, presence and localization of distant metastases as well as system disturbances caused by paraneoplastic syndromes. For example, central LC is characterized by cough, hemoptysis, temperature rise, shortage of breath, fever and productive cough as a consequence of paracancerous pneumonitis. In peripheral cancer, pain in the thorax, cough, shortage of breath and symptoms of lung abscess (in case of tumor necrosis) come to the foreground.

5.1 Pathologic Anatomy and Mechanisms of Metastases

Presently it is accepted to use the clinical-anatomical and pathomorphological classifications to characterize diverse forms of LC (Tyulyandin and Moiseenko 2004).

5.1.1 Clinical-Anatomical Classification of LCs

Central Cancer of the Lung

- Endobronchial
- Peribronchial nodal
- Branched

Peripheral Cancer of the Lung

- Odal
- Pneumonia-like (bronchioloalveolar)
- Cancer of the lung apex (Pancoast syndrome)

5.1.2 Histological Classification of the WHO (1981)

- Dysplasia/carcinoma in situ
- Planocellular cancer (30%)
- Small cell cancer (18.2%): oat cell cancer, transitional cell cancer
- Adenocarcinoma (30.7%): acinar, papillary, bronchioloalveolar, solid cancer with mucin formation
- Large cell cancer (9.4%): giant cell cancer, clear cell cancer
- Glandular-planocellular (1.5%)
- Carcinoid tumors (1.0%)
- Cancer of the bronchial glands (9.2%): mucoepidermoid, adenocystic and others

In 52% of cases the malignant neoplasm is situated in the right lung, and in 48% of cases it is in the left lung. The spread of LC occurs in three ways: lymphogenous, hematogenous and implantation. Among regional lymph nodes, the intrathoracic (mediastinal and intrapulmonary), prescalenic and supraclavicular nodes are the first to be tumor-involved. In case of hematogenic metastasis, the brain, bones, suprarenal glands, contralateral lung, liver, pericardium and kidneys are affected. The implantation spread manifests itself with lesions of the pleura with development of carcinomatosis and cancer pleuritis.

5.2 Methods of Diagnosis

The detection of LC is possible at screening and additional examinations. The widest-spread kind of screening examination is prophylactic fluorography. It is meant to reveal a symptom group whose nature is specified at further additional patient examination. The algorithm of additional patient examination consists of four stages:

1. The preliminary stage consists in doing survey (diagnostic) fluorography or roentgenography of the thoracic organs in frontal and lateral projections.
2. The tomographic stage includes performing MSCT in order to examine tumor dissemination.
3. The bronchologic stage consists in cytological examination of phlegm and in fiberoptic bronchoscopy.
4. The differential diagnosis stage includes roentgenoscopy, transthoracic puncture (aspiration) biopsy, bronchography, bronchoscopy, angiography, thoracoscopy, mediastinoscopy, MRI, diagnostic thoracotomy.

It should be noted that despite the wide spectrum of modern methods of clinical diagnosis and radiodiagnosis, the problem of differential diagnosis of solitary lung masses (SLMs) is still unresolved. SLM is a node in the pulmonary parenchyma with diameter less than 3 cm, which has clear boundaries, a round or oval form. Every year up to 13,000 new cases of SLM are detected. Additionally, 50–60% of patients are subsequently diagnosed with a malignant lung lesion. In the remaining cases, the pathologic process is based on benign granulomas, local pneumofibrosis as well as hamartomas and alterations conditioned by tubercular process.

The correct assessment of clinical-radiological data in patients of this category will permit unnecessary surgery to be avoided. Currently, when SLM is detected, especially in young patients, expectant management is adopted. At the same time, according to Yankelevits et al. (1997), absence of growth of pathologic nodes only in 65% of cases suggests the benign character of changes.

5.2.1 PET Diagnosis

The role of PET in LC diagnosis is ambiguous. On the one hand, the method is highly sensitive and permits visualization of malignant neoplasms of the lung. On the other hand, the nature of detected changes cannot always be defined by means of ^{18}F -FDG PET. The main cause of diagnostic problems is the absence of pathognomonic PET signs permitting discrimination of tumor lesions from inflammatory changes (Baum et al. 2002). For example, according to Gould et al. (2001) who implemented analysis of 1474 SLM cases, the sensitivity of the method was 96%, its specificity being only 74%. The results of other researchers indicate that the sensitivity of the method ranges within 82–100% and its specificity varies from 63% to 90% (Bury and Rigo 2000; Kubota et al. 1990; Lowe et al. 1994; Partz et al. 1994). A diagnostic advantage of PET/CT versus PET in diagnosing lung cancer is not clearly proofed. Metaanalyses of the rare papers indicate an increase of sensitivity and decrease of specificity (woolley 2008).

The widest spread cause of false-negative results in PET examination is the small size of formation (less than 5 mm). At the same time, according to Herber et al. (2004), the efficiency of PET in diagnosis of solid lung masses with size up to 1 cm is higher than that of CT. They report that PET sensitivity makes up 93%, its specificity is 77%, positive prognostic value is 72% and negative prognostic value is 94%. Another cause of false-negative results is isometabolism of ^{18}F -FDG in cases of some histological tumor types. For example, bronchoalveolar tumor (BAT), mucinous adenocarcinoma, carcinoid masses and metastases of thyroid cancer and of renal cell cancer may not be diagnosed with help of PET. The absence of pathological radiopharmaceutical (RP) accumulation in malignant neoplasm can be caused by the high differentiation of cell structures and consequently by the low biological activity of tumor. This is why negative PET results in LC patients usually imply a favorable disease prognosis (Schiepers et al. 2002). However, it should be noted that in most cases the absence of pathological ^{18}F -FDG uptake in the projection of a solid mass visualized in X-ray denotes a benign process (Mavi et al. 2005; Vansteenkiste et al. 2004). According to Lowe et al. (1994), only 5% of patients with negative PET results are subsequently diagnosed with LC. In connection with these data the authors conclude that the accuracy of the method in differential diagnosis of LC, benign neoplasms and chronic inflammatory diseases in the remission stage may reach 95% (Fig. 5.1).

The analysis of scientific literature of the last years shows that there are many works concerning the pathophysiological characteristics of high ^{18}F -FDG uptake in the area of inflammation. It has been proved that standardized uptake values (SUVs) in acute and chronic infectious states range within large limits. In some cases the

Fig. 5.1 MSCT and PET data in patients with pneumosclerosis (a, b) and thromboembolism of small pulmonary artery branches of the basal segments of the right lung (c, d)

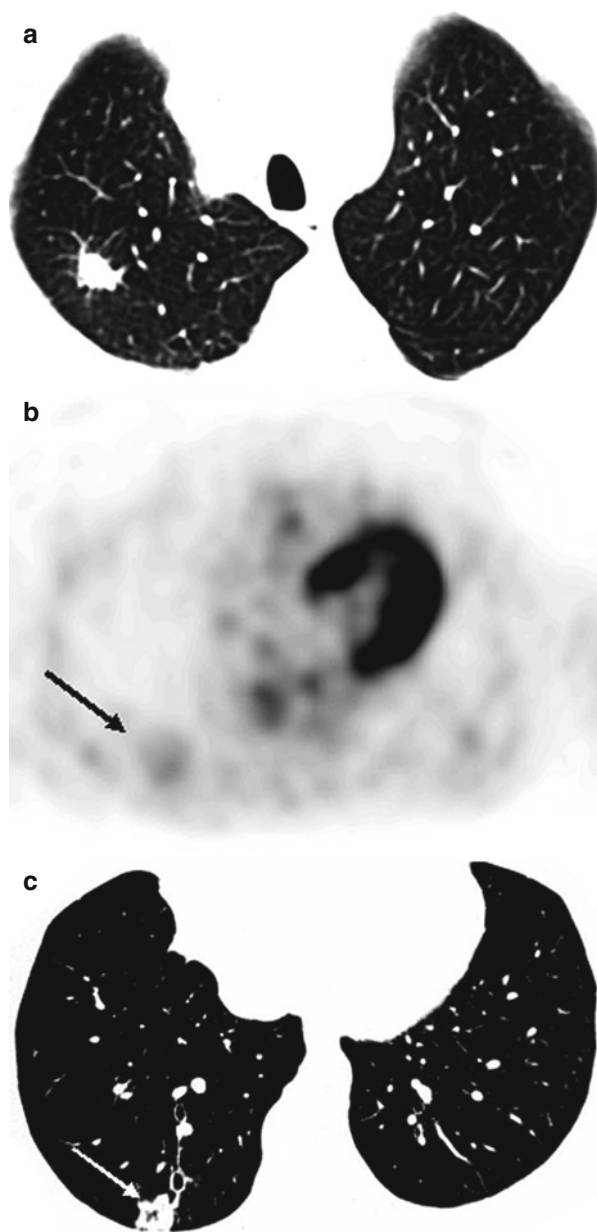
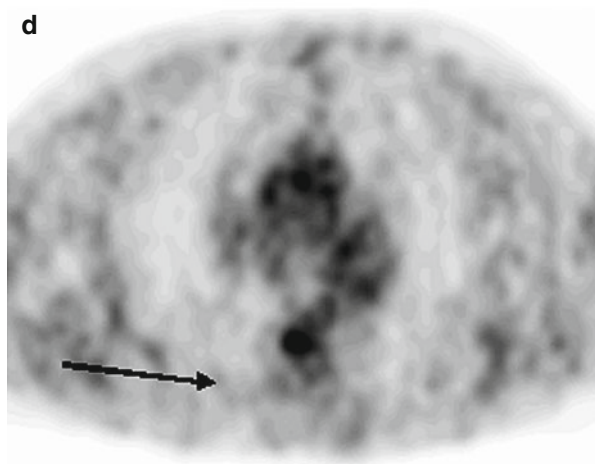
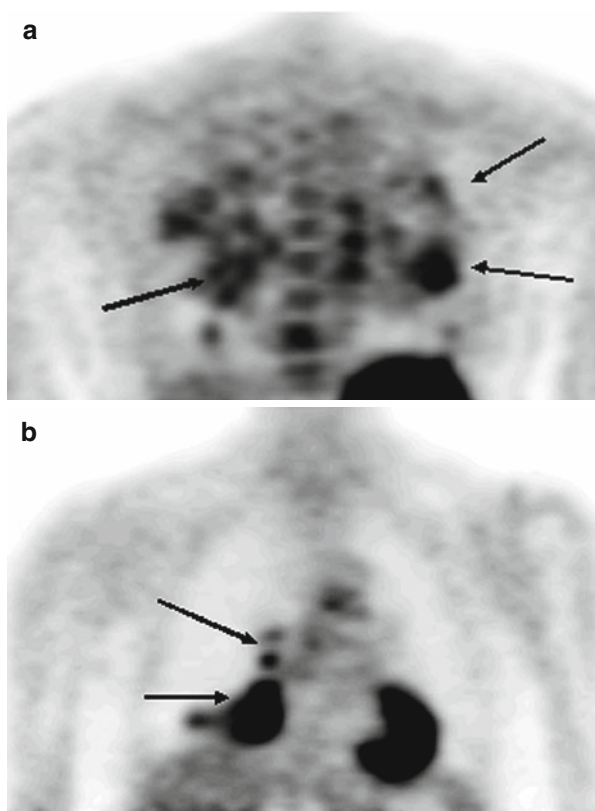
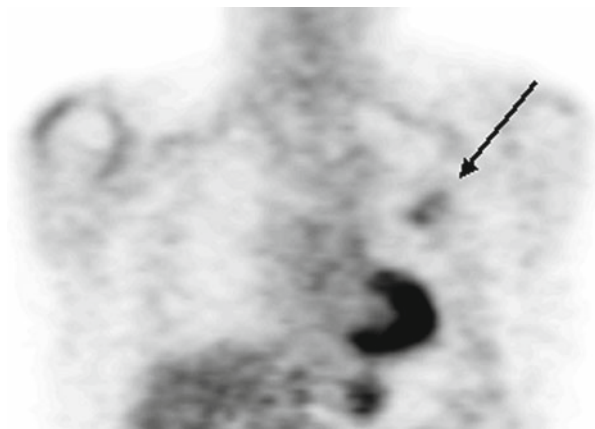


Fig. 5.1 (continued)**Fig. 5.2** PET results in a patient with generalized sarcoidosis (a) and in a patient with tuberculosis of the right lung (b)

intensity of RP accumulation in tumor can be lower than in inflammation. Most often such a situation is observed in granulomatous lesion of pulmonary parenchyma (Fig. 5.2).

Fig. 5.3 PET data in a patient with bronchial pneumonia



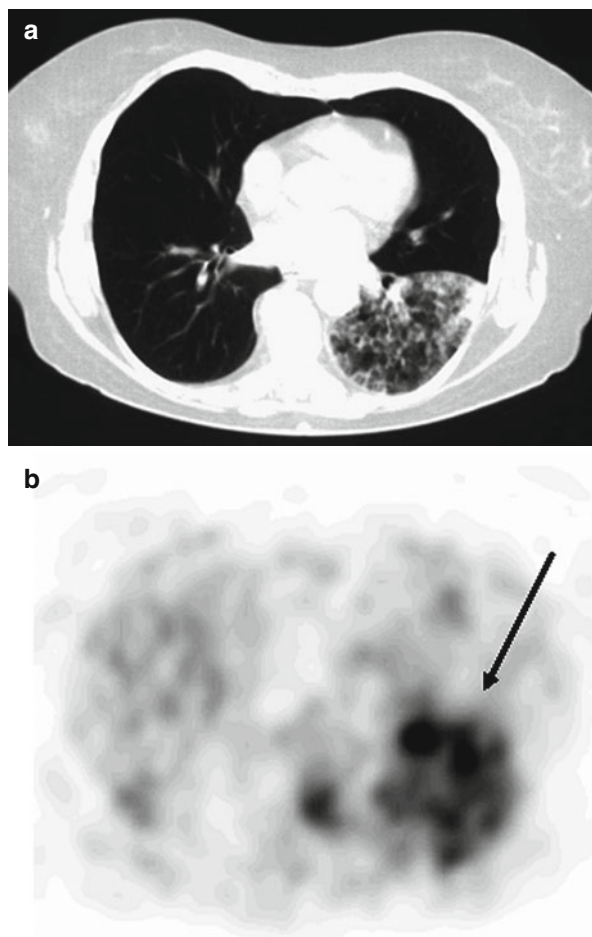
In pneumonia of bacterial or viral genesis, SUVs are not usually high (Fig. 5.3). However, it should be taken into account that low SUVs may be detected in some histological types of malignant tumors (Fig. 5.4). Small-sized masses are also characterized by low SUV values in consequence of the volume averaging of the intensity of RP accumulation since absolute ^{18}F -FDG accumulation is observed in the area of minimum spatial resolution.

One of the methods of correcting the resolution effect is, according to Hickeson et al. (2002), calculating SUV considering the diameter of formation as measured at CT examination. As a result, the authors argue, the diagnostic accuracy of PET in detecting small lung masses (less than 1 cm) increases from 58% to 89%.

In order to solve diagnostic problems arising in differential diagnosis of solid lung masses, some authors suggest using a threshold value of SUV equal to 2.5 (Ghesani et al. 2003). In their opinion, in cases when SUV exceeds the indicated value, detected changes should be considered as malignant. The sensitivity of the method in this research made up 92%, its specificity was 90%, positive prognostic value was 92%, negative prognostic value amounted to 90%, and total diagnostic accuracy was 91%.

Currently, much interest is aroused by the results of the use of delayed scanning for differentiating LC from inflammatory changes. Delayed PET (1 and 2 h after RP introduction) was first implemented by Hustinx et al. in 1999 in patients with malignant head and neck tumors and in those with inflammatory changes. In malignant tumors an increase in SUV rates of more than by 12% was detected by the authors. At the same time, SUVs calculated in the area of inflammation and normal anatomic structures (tongue, larynx) did not significantly change. Another group of authors also performed delayed PET in vitro, in animals and in humans (Zhuang et al. 2003). The obtained results indicated an increase of SUV in malignant tumors. Based on these results, the authors think that the use of delayed PET may be a method of differential diagnosis between malignant and benign neoplasms. Similar work was done by Nakamoto et al. (2000) in examining patients with solid lung masses. Scanning was done 60 and 120 min after the introduction of RP. This author also

Fig. 5.4 MSCT (a) and PET (b) results in a patient with bronchoalveolar carcinoma



observed an increase of SUV levels in LC patients and absence of significant dynamics in patients with inflammatory changes (Fig. 5.5). Delayed PET, 60 and 90 min after introducing RP, was also applied by Matthies et al. (2002). An increase of SUV no less than by 10% was detected in all the patients examined. The sensitivity of the method in this research made up 100%, its specificity was 89%.

Afterwards Kung et al. (2004) studied the capabilities of delayed ^{18}F -FDG PET in patients with non-small cell cancer. Scanning was done 1, 2, 4 and 6 h after the introduction of RP. The obtained results showed better contrast between tumor and normal pulmonary parenchyma as well as growing SUVs towards the end of 4 h. Within the lapse between 4 and 6 h after the injection of RP SUVs did not significantly change.

So, it becomes obvious that the capacities of ^{18}F -FDG PET in differential diagnosis of LC, benign tumors and inflammatory changes are still not exhausted, and

Fig. 5.5 Results of PET done 120 and 240 min. after RP injection: (a, b) in a patient with lung cancer (c, d), in a patient with bronchial pneumonia

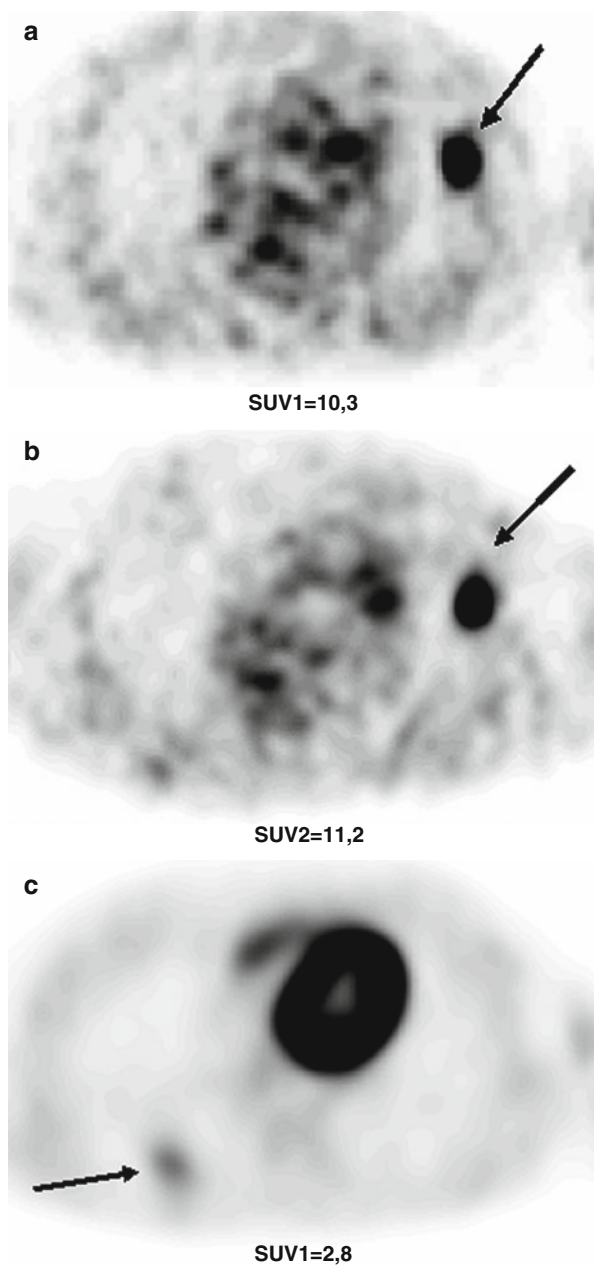
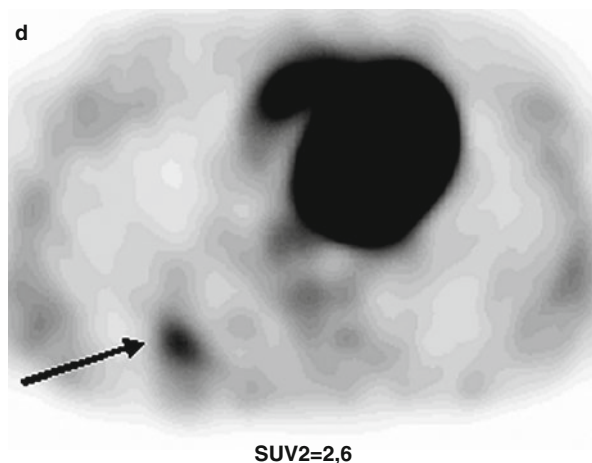


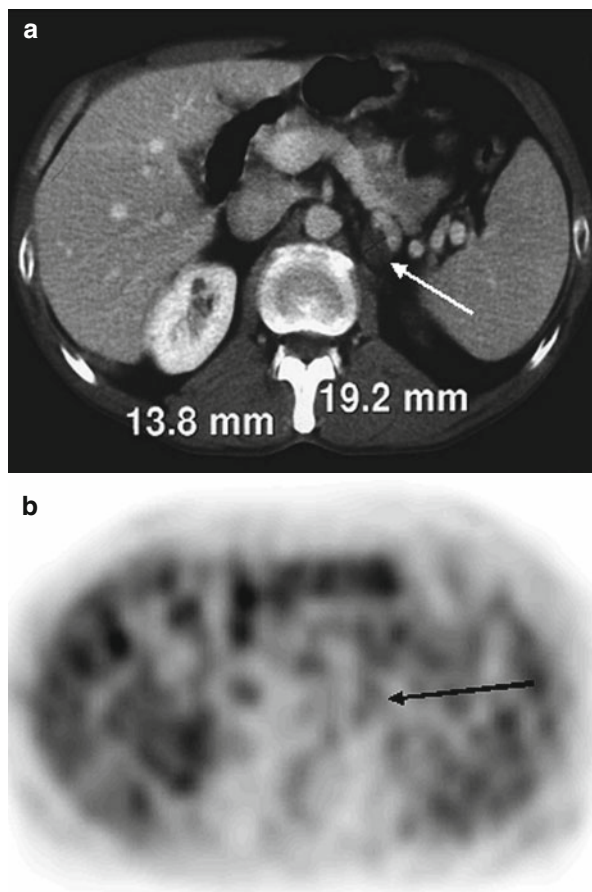
Fig. 5.5 (continued)

further study of delayed PET should be considered as a topical and promising issue.

The role of ^{18}F -FDG PET in assessing tumor dissemination is crucial. The results of numerous studies point out the advantages of PET over CT in the diagnosis of metastatic lesions of the lymph nodes of the mediastinum and of the bronchopulmonary lymph nodes. The main weak point of CT in determining the involvement of a lymph node in the tumor process is in assessing its size. Normally the diameter of a lymph node of the mediastinum at CT examination should not exceed 1 cm, and that of the root of lung 0.7 cm. According to some data, this approach in 21% of cases induces false-negative diagnosis in assessing lymph nodes with sizes less than 10 mm. At the same time, there are false-positive conclusions in 30–40% of patients with lymph node diameters larger than 20 mm. As a result, the sensitivity of CT is 60%, its specificity is 77% and its diagnosis accuracy is 65% (Weber et al. 2003). On the contrary, Gould et al. (2001) implemented metaanalysis of PET results and thereby defined PET sensitivity as 85–90%, and specificity as 81–100%. Additionally, these authors stress that the high negative prognostic value of the method (~93%) in diagnosing metastatic lesion of the lymph nodes of the root of the lung permits omission of implementing mediastinoscopy. The role of PET/CT for a further improvement of these statistics is ambiguous. A metanalysis of actual literature shows a wide spread of results in sensitivity, specificity and positive predictive value of 44–93%, 40–92% and 29–71% respectively (Chao 2012, Li 2012, Kumar 2011 and Bille 2009). This may depend on the design of the studies and a predefined SUV cutoff for pathologic, meaning malignant, metabolic activity in the lymph nodes.

The possibility of obtaining a whole-body image in PET is the main advantage of this method. It becomes possible to assess at a single examination the state of lymph collectors of virtually all the anatomic regions, the pleura and liver, the supra-renal glands and osseous system. As stated by different authors, PET permits restaging of the disease in 25–40% of cases (Baum et al. 2002; Deichen et al. 2003; Valk et al. 1995).

Fig. 5.6 MSCT (a) and PET (b) data in a patient with benign hyperplasia of the left adrenal gland



The widest spread and still crucial problem in clinical staging of the LC is diagnosing metastatic lesions of suprarenal glands. As a rule, in CT it is not possible to carry out differential diagnosis between adenoma or hyperplasia of the suprarenal gland and secondary alterations in the parenchyma of the organ. PET is a highly informative method permitting to differentiate between benign and malignant processes in the suprarenal gland (Fig. 5.6). The sensitivity of PET in differentially diagnosing suprarenal space-occupying lesions may reach 100% and its specificity is 94%. As for diagnosing a metastatic lesion of the bones, PET is a less sensitive radiodiagnostic method than skeleton scintigraphy. However, PET specificity is higher (Zhuang et al. 2003).

Most researchers observe the growing role of PET in planning radiotherapy of central LC due to the high diagnostic accuracy of the method in differentiating areas of atelectasis, fibrosis and malignant lesion. According to some data, PET may facilitate the correction of fields of radiation in 30–40% of cases (Baum et al. 2002). Additionally, the unquestionable advantage of the method is the possibility of early

treatment efficiency evaluation. Weber et al. (2003) performed ^{18}F -FDG PET in patients with planocellular LC before treatment and after two courses of polychemotherapy. In all the cases of complete metabolic regression of tumor, no signs of tumor relapse were detected in patients during the first year of dynamic observation. At the same time, malignant generalization was observed in patients with a partial tumor response and metabolic progression of LC. Presently, high diagnostic accuracy of PET in detecting local relapses is ascertained. According to some data this index reaches 91% (Baum et al. 2002).

In order to avoid false-positive results, PET examination should be implemented no sooner than 2 months after surgery and 3–4 months after radiotherapy. Interesting results have been obtained by a group of Japanese authors. The researchers compared SUVs measured in tumors with expression of P-glycoprotein (multidrug-resistance gene product) and without it. Statistical data processing confirmed a correlation between these indices. The authors think that the obtained results may be used for the prognosis of chemotherapy.

The reported data confirm the high efficiency of ^{18}F -FDG PET in diagnosis, differential diagnosis, clinical staging and treatment efficiency evaluation in cases of LC. Particularly valuable data can be obtained when it is necessary to identify solitary lung masses unrelated to an acute inflammatory process (pneumofibrosis, benign tumors). In difficult diagnostic situations it is appropriate to have recourse to delayed scanning. In a number of cases it can improve the quality of images and permit differential diagnosis of solid lung masses to be carried out. Also, as world experience shows, PET results may have a radical impact on restaging LC and consequently on treatment optimization.

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Esophageal cancer (EC) is in sixth place in terms of oncological morbidity. In recent years in Russia, a tendency toward a reduction in frequency has been observed. The disease is most often found in elderly men. Before 30 years of age EC is relatively rare. Considerable heterogeneity in geographic distribution of the disease is registered. Particularly high EC morbidity rate is observed in countries of Central Asia, where it exceeds by 10–12 times that in the south-west and west of Russia (Merabishvili 2006).

Increase in EC morbidity is influenced by the following factors: regular consumption of hot, coarse and ill-chewed food and alcohol, smoking, chronic inflammatory processes accompanied by cicatrice formation (burn strictures, esophagites accompanying hernia of the esophageal opening, diverticula, reflux-esophagitis, Barret's esophagus, leukoplakia, sideropenia and benign esophageal polyps (Gantsev 2004).

Among early EC symptoms there are: progressive worsening of the patient's general condition, lowering of the appetite, growing general weakness, lowering of ability to work, weight loss. Deglutitive disturbance and dysphagia occur in later stages of development of the tumor process. According to A. Savitsky's classification, it is accepted to distinguish four grades of dysphagia:

Grade I – aglutition occurring during passage of solid food (bread, meat) through the esophagus

Grade II – aglutition when intaking porridge-like and semi-liquid food

Grade III – aglutition when drinking liquids

Grade IV – complete esophageal obstruction

Pain in the area of the thorax, hoarse voice and sensation of food lump should be also considered as late symptoms of the disease.

6.1 Pathologic Anatomy and Mechanisms of Metastases

The frequency of tumor lesion of different anatomic areas of the esophagus is various. Cancer of the cervical section of the esophagus makes up 10%, that of the thoracic section is 60% and for the esophagogastric section it is 30%.

Three forms of EC are distinguished:

- The ulcerous form (saucer-like and crateiform cancers) grows exophytically into the lumen of the esophagus, primarily lengthwise.
- The nodal form (fungoid and papillomatous cancers) has the appearance of a cauliflower and obturates the lumen of the esophagus; in necrosis it may look like ulcerous cancer.
- The infiltrate form (scirrhous and stenosing cancer) develops in the submucous layer, encircles the esophagus, and manifests itself as a whitish, dense mucous membrane on which ulcerations may occur; in stenosing cancer, circular growth prevails over lengthwise growth.

In 97–99% of cases, EC is planocellular with or without cornification.

The first stage of metastasis in EC occurs primarily in the lymphogenous way. The well-developed lymphatic system in the submucous layer of the organ conditions intramural dissemination of tumor process, sometimes at 4–10 cm from the primary formation.

The second stage of metastasis has its own laws and depends on the situation of the primary formation:

1. In cancer of the cervical section of the esophagus, prescalene, internal jugular, superior and inferior cervical, periesophageal and supraclavicular lymph nodes are affected.
2. In cancer of the thoracic section of the esophagus, superior and inferior periesophageal and tracheobronchial lymph nodes are affected.
3. In cancer of the esophagogastric section, inferior periesophageal, phrenic, pericardial, celiac lymph nodes as well as those situated along left gastric arteries are affected.

Since the lymphatic vessels of the esophagus flow directly into the thoracic duct, in some cases metastatic lesion of the lymph nodes of the lesser omentum may be observed, as well as that of lymph collectors situated along the left gastric artery, neck and supraclavicular areas. Distant lymphohematogenous metastases of the EC are observed in the liver, lungs and bone system.

6.2 Methods of Diagnosis

Esophagoscopy is an obligatory examination method in EC. A negative result of esophagiscopy is not a sufficient reason to exclude EC diagnosis. A small tumor or ulcer is sometimes difficult to observe, since the extended esophageal wall above the site of lesion may overhang and obturate the pathologic formation. In case of tumor growing infiltratively along the submucous layer, esophagoscopy sometimes detects only the narrowing of the esophagus and hindered passage of the tube. In case of this kind of growth, biopsy results may be negative too.

Tracheobronchoscopy is done in order to diagnose the invasion of esophageal tumor to the bronchus. When invasion symptoms are detected, morphological study is carried out obligatorily.

X-ray permits determination of the form of tumor growth, its localization and extension. The main X-ray signs of EC are: disturbance of landscape structure of the esophageal mucous membrane, filling defect, tumor stain, and absence of peristalsis of the esophageal wall. The earliest and most difficult to detect symptom is absence of peristalsis. In some cases this sign can be the only one and can persist for a long time. Later on, other symptoms manifest themselves: restructuring or destruction of the landscape of the mucous membrane declaring itself by the atypical form and situation of folds, formless deposits of contrast substance or minor areas of clarification.

In order to specify the limits of extra-esophageal dissemination of malignant neoplasm, roentgenography and computed tomography (CT) are used in the presence of pneumomediastinum. For the purpose of detecting regional as well as distant metastases, recourse is had to ultrasonography (US) and CT (Shalimov et al. 2000; Satsukevich 2003).

6.3 Staging

Clinical staging in EC is done according to the international TNM classification, which reflects three obligatory components: the size and depth of primary tumor invasion, metastasis to regional lymph nodes and metastasis to distant organs.

6.3.1 PET Diagnosis

6.3.1.1 T Category

Positron emission tomography (PET) sensitivity in diagnosing EC, according to different authors, varies within the range of 77–100% (Cook and Maisey 1996; Devesa et al. 1998; Shreve et al. 1999; Kato et al. 2002). According to Fucunaga et al. (1998), who examined 48 patients with esophageal adenocarcinoma, PET sensitivity was 98%. Researchers observe that in a considerable number of patients the standardized uptake value (SUV) index was higher than 2.0 and averaged 6.99 ± 3.05 . Meanwhile, the SUV in the normal esophagus did not exceed 1.34 ± 0.37 . In this context, these authors consider PET to be an efficient method of diagnosing EC. The most frequent factors that make it difficult to interpret PET data include the insufficient visualization of anatomic structures of the mediastinal organs and the impossibility to determine the depth of lesion of the esophageal wall and tumor relations to adjacent organs. Even in the middle part of mediastinum PET/ CT allows the clear anatomic spatialisation of pathologic RF activity to the oesophagus (Fig. 6.1). False-negative results are usually induced by the small size of the primary esophageal mass and high tumor differentiation. False-positive results may occur due to high radiopharmaceutical (RP) accumulation in the area of esophagites, diverticula and in Barret's esophagus. However, low SUVs in the area of benign changes and careful study of clinical and radiological data in most cases permit to differentiate between inflammation and a malignant process (Bytzer et al. 1999; Rankin et al. 1998).

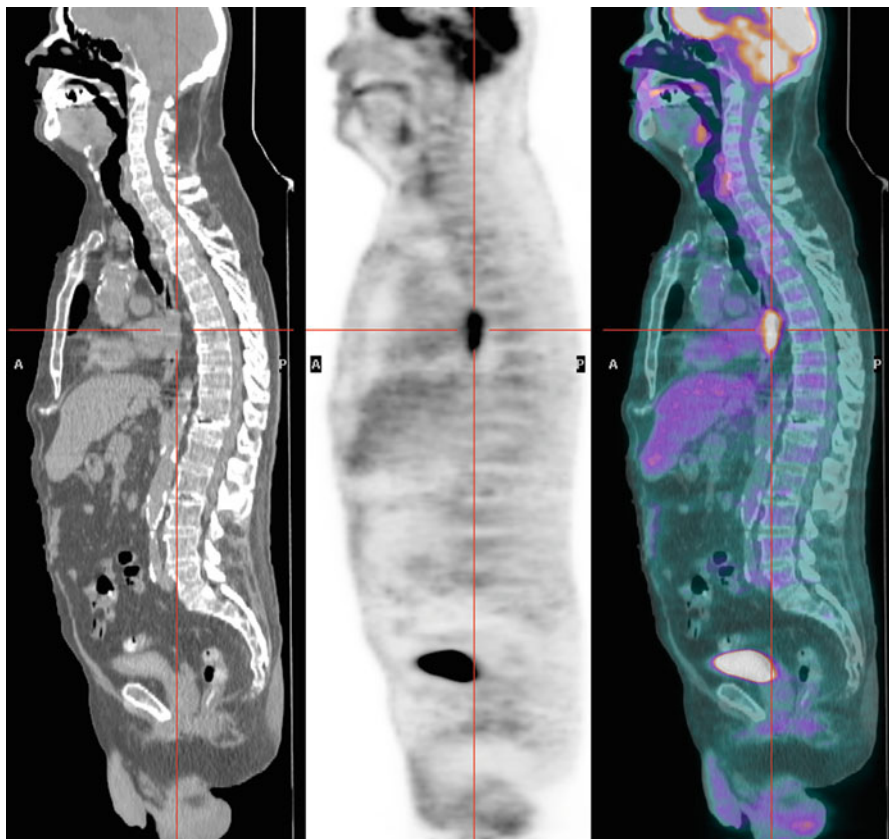


Fig. 6.1 ^{18}F -FDG PET/CT of a patient with esophageal cancer in the middle segment (marked)

6.3.1.2 N Category

PET sensitivity in detecting metastatic lesions of regional lymph nodes in EC cases depends on the stage of the disease according to T category and ranges from 22% to 94%, the specificity being 78–100% (Block et al. 1997; Lerut et al. 2000; Yoon et al. 2003). False-negative results may be obtained in case of small size of affected lymph nodes (less than 1 cm) or as a consequence of their image merging with the contours of the primary formation. False-positive results are most often conditioned by concomitant pathology of the lymphatic system; for example, by granulomatous inflammation in sarcoidosis.

6.3.1.3 M Category

The diagnostic accuracy of ^{18}F -FDG PET in detecting distant metastases in EC is 89–96%, depending on their anatomic situation. Use of PET in preoperative staging permits the detection of additional foci in 37.5% of cases, which in most cases

induces a change in therapeutic management (Flanagan et al. 1997; Kole et al. 1998; Luketich et al. 1997; Bruzzi et al. 2007).

6.3.1.4 Treatment Efficiency Evaluation

Statistical research in recent years has shown that the 5-year survivability of EC patients after radical surgical intervention does not exceed 30–50%. This is due to relapse occurring most often locally in the area of anastomosis or in the cellular tissue of the mediastinum. In the remaining cases, metastatic lesion of the liver, lungs and bone system is detected. The diagnostic accuracy of ^{18}F -FDG PET in detecting local EC relapse was 91–96% (Cook and Maisey 1996; Couper et al. 1998; Shreve et al. 1999). The most frequent cause of false-positive results is high RP accumulation in the area of anastomosis and balloon expansion of anastomotic structures. However, observing time intervals between PET examination and surgical operation in most cases permits the avoidance of diagnostic difficulties.

The diagnostic accuracy of PET in differentiating between post-radiation changes and viable tumor tissue exceeds that of CT and is at a level of 93%. However, in order to avoid false-positive results, PET examination should be implemented no earlier than 4–6 weeks after the end of radiotherapy (Couper et al. 1998).

Results obtained by Jang et al. (2002) look interesting and promising. The researchers studied the prognostic role of the method in EC patients with different stages of the disease. Observation of patients was carried out for 26 months. The authors observed that high SUVs in the initial forms of the disease are in direct correlation to survivability. Meanwhile, such a correlation was not observed in patients in the 3rd to 4th stages of tumor progression.

We conclude that PET is an auxiliary method of radio-visualization in diagnosing EC. At the same time, this method shows high efficacy in disease staging and restaging as well as in treatment efficiency evaluation.

Suggested Reading

Vazhenin AV, Voronin, MI, Vaganov NV et al (2003) Radiodiagnosis and radiotherapy: a textbook for medical students, residents and interns. Moscow (in Russian)

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Stomach cancer (SC) is one of the most frequent forms of malignant tumors of the gastrointestinal tract. About one million persons develop SC annually in the world. In the Russian Federation SC is the third most common among all oncological diseases, after lung cancer and skin cancer. It is most often older people (50–60 years old) who develop SC. Up to 25% of registered SC cases fall in the age range of 40–50 years (Merabishvili 2006). The etiology of this disease still remains unknown. However, the results of experimental studies and data of epidemiological research have revealed some predisposing factors as well as precancerous states. Among predisposing factors leading to SC, there are: diet with excess of common salt provoking osmotic lesion of epithelium and facilitating contamination of mucous membrane with *Helicobacter pylori* bacteria, smoking, regular use of alcohol and hereditary susceptibility to carcinogenic influence. The main precancerous diseases are chronic gastritis, stomach polyposis and chronic ulcer (Gantsev 2004).

At the beginning of development of SC, clinical symptoms are extremely diverse and marked pathognomonic signs are absent. Disease manifestations are usually limited to generalized symptoms: weakness, lower ability to work, lowering or loss of appetite, gastric discomfort, progressing apparently causeless weight loss. Late symptoms entirely depend on the anatomic situation of the tumor, form of the mass and its rate of growth and metastasis. In cancer of the antral section, for example, a sense of repletion, bitter eructation, and vomiting just after having eaten food are characteristic. As the tumor grows, these symptoms increase too. Cancer of the cardiac part does not manifest itself for a long time and occurrences of dysphagia appear only as the stomach entry narrows and the tumor process expands to the oesophagus. In cancer of the body of the stomach, weakness, anemia, lowering of appetite and depression come to the foreground. Stenosis occurrences and marked painful sensations appear in case of significant tumor dissemination when the tumor expands to the antral or cardiac sections of the stomach. Long asymptomatic course is also characteristic of cancer of the fundus of the stomach. Clinical manifestations appear only when the diaphragm and pleura are affected by tumor (Vazhenin et al. 2003; Shalimov et al. 2000).

7.1 Pathological Anatomy and Mechanisms of Metastases

The classification put forward by Bormann in 1926 has received the widest use for morphological characteristics of SC. It distinguishes four anatomical types of SC:

Type 1 – polypoid and fungoid circumscribed cancer with exophytic growth.

Type 2 – cup-shaped and saucer-shaped cancer with clearly contoured boundaries and cylinder-like raised edges, which is considered as destructive form of polypoid cancer.

Type 3 – ulcerous-infiltrative, ulcerating or ulcer-like cancer, whose tissue is not clearly delimited from the surrounding stomach wall.

Type 4 – diffuse cancer characterized by the thickening of the entire stomach wall; a marked form of endophytic fibrous cancer (scirrhus) is linitis plastica. In this stage of tumor, the stomach has the shape of a thick-walled tube from the pylorus to the cardiac orifice.

The histological structure of SC is characterized by large diversity, which has given rise to numerous classifications. In order to unify the data, the international WHO classification was drawn up in 1977 and is still used. It distinguishes non-differentiated cancer, signet ring cell carcinoma of the stomach, mucous adenocarcinoma (colloid cancer), glandular-planocellular cancer, planocellular cancer, and unclassified tumors. It should be noted that this classification does not have any prognostic significance.

Metastases in SC occurs in three ways: lymphogenous, hematogenous and by implantation (dissemination through peritoneum). Most often, dissemination takes place in the form of different combinations of the indicated ways, lymphogenous metastasis being principal.

Presently it is considered that metastatic changes in lymph nodes appear in the following sequence:

1. Lesion of regional lymph nodes situated in the gastric ligaments
2. Infiltration of lymph nodes accompanying big arteries
3. Secondary lesion of retroperitoneal lymph nodes and organs of the abdominal cavity

SC metastasizes via the hematogenous route to the liver, lungs, adrenal glands, bones and hypodermic cellular tissue. Implantation metastases are formed during contact transfer of tumor cells through the peritoneum in the form of small military eruptions – carcinomatosis. Krukenberg metastases (to the ovary), Virchow's metastasis (to the left supraclavicular lymph nodes), Sister Mary Joseph's nodule (to the navel) are also examples of secondary implantation changes; in the advanced stages of cancer, metastatic lesion of pararectal cellular tissue of the fundus of the small pelvis (Schnitzler metastasis) may occur.

7.2 Methods of Diagnosis

Radiological examination is one of the classic methods of detecting SC but it's importance decreased over the last decades according to the rise of CT, US and Gastroscopy. Among the most important radiological symptoms there are: filling

defect, loss of elasticity, tensility of the stomach wall leading to the absence of peristalsis of the stomach in the area of tumor lesion, change in the stomach landscape in the site of the malignant formation.

However, all the mentioned symptoms are typical of the late stages of SC when tumorous lesion has a disseminated character. Meanwhile, detecting and differentially diagnosing the initial forms of SC based on the radiological examination of the stomach is still a difficult, sometimes unsolvable task. This is due to the fact that at the onset of the disease tumor process is limited to the mucous membrane and does not expand to the submucous layer; it is in the form of flat erosion, defined as a low-intensity spot with unclear contours.

Fibrogastroscopy (FGS) is today the leading examination method when SC is suspected; it permits determination of the character of tumor growth and localization, as well as to obtain material for performing cytological or morphological examinations. The main advantage of the method over radiological examination is the possibility to detect early forms of SC in 90% of cases. At the same time, complex examination of the stomach (both radiological and gastroscopic) increases the diagnostic accuracy up to 96.7%.

The use of ultrasound (US) in diagnosis of SC was described as far back as 1976 in studies by Lutz (1976) and coworkers, who observed that the circular narrowing of a hollow organ is a precondition for visualizing tumor in it. An important role is assigned to US in case of lesion of the stomach wall caused by neoplasms with infiltrative growth type, especially by lymphomas not leading to the ulceration of the mucous layer which makes their detection difficult in FGS. Tumors of the antral sector are better visualized, while those of the body of the stomach are visualized worse. The diagnostic accuracy of transabdominal US in assessing the degree of invasion of the stomach wall is 84%. However, in case of a local change in the stomach wall, sometimes up to 40 mm long, especially in hypersthenic patients, false-negative results may be obtained. This reduces the diagnostic value of the method in the initial stages of SC (T1 and T2).

The capacity of computed tomography (CT) in determining the depth of tumor invasion into the stomach wall is ambivalent. On the one hand, this method does not allow the differentiation of the submucous and muscular layers of the stomach in degree of invasion (T1 and T2). On the other hand, it has significant diagnostic capacities in detecting tumor infiltration of subserous and serous membranes and in determining the degree of tumor expansion to adjacent anatomic structures (T3 and T4). Diagnostic difficulties may arise in case of insufficient visualization of the stomach wall in asthenic patients due to feebly marked fatty cellular tissue.

Performing CT, US and MRI examinations is necessary in order to assess the dissemination of the tumor process. All these methods permit determination with nearly the same diagnostic accuracy tumor relations with adjacent anatomic structures, which is of much practical importance. However, the diagnostic accuracy of CT and US in detecting metastatic lesion of lymph nodes does not exceed 88%. The main source of diagnostic difficulties is the absence of pathognomonic signs of metastatic lesion and reactive hyperplasia of the lymph node. It is only the enlargement of lymph nodes up to more than 20 mm, their confluence into one conglomerate and unclear image of the capsule that convincingly indicate alterations of metastatic nature (Satsukevich 2003).

7.3 Staging

Clinical staging in SC is done according to the international TNM system, which reflects three obligatory components: the depth of invasion of the primary tumor, metastasis to regional lymph nodes and metastasis to distant organs.

7.3.1 PET Diagnosis

7.3.1.1 T Category (TNM)

The sensitivity of ^{18}F -FDG PET in diagnosis of malignant neoplasms of the stomach largely depends on the degree of tumor dissemination inside the organ. For example, if the tumor is 2–4 cm large, the sensitivity of the method does not exceed 61%, if its size is 4 cm or more the sensitivity may reach 86% (Kole et al. 1998). Also, many authors observe that the possibility of visualizing a malignant neoplasm of the stomach is largely determined by the histological type of the tumor (Czech et al. 2000; Roukos and Kappas 2002; Valk et al. 2006). For example, PET sensitivity for epithelial carcinomas is higher than for non-epithelial ones. False-negative results may be obtained in patients with mucinous adenocarcinoma and carcinoid tumors. According to the results of studies, PET sensitivity for these types of SC does not exceed 65%. At the same time, according to Yoshioka et al. (2003) the 2-year survivability in cases of PET-positive tumors of the stomach is 66%, and in case of PET-negative tumors it is 94% (Fig. 7.1).

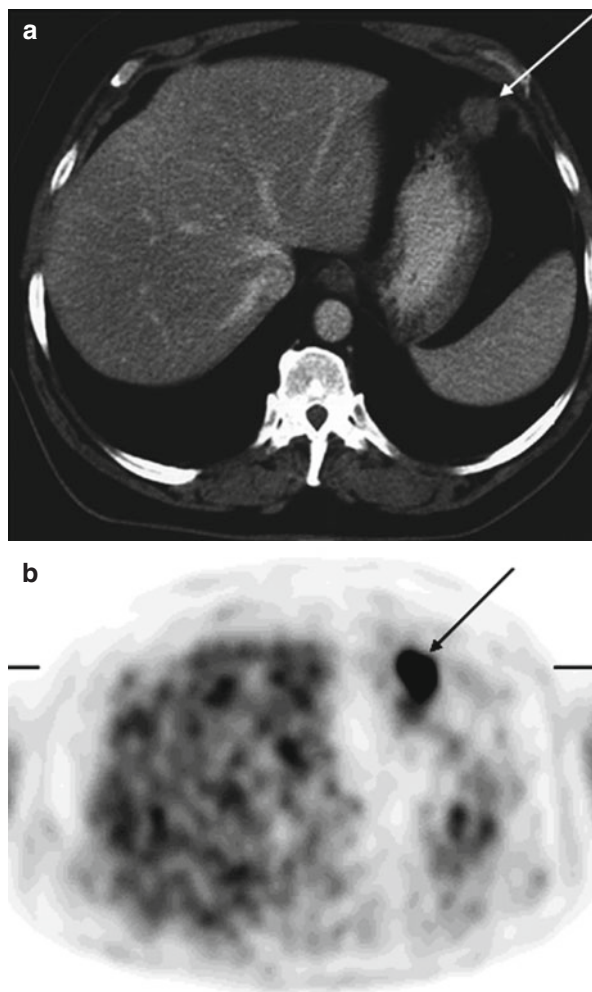
During PET examination of the stomach, physiological uptake of RP in the smooth musculature of the organ is usually observed, which has a diffuse character and in many cases makes diagnosis of SC difficult. The most frequent cause of high RP uptake consists of inflammatory alterations (gastritis, gastroduodenitis, and ulcer of the stomach). RP uptake of a focal or diffuse character may also be observed in patients with adenomatous or hyperplastic stomach polyps as a consequence of peritumoral inflammation. Such a situation may lead to both false-negative and false-positive results. In particular, in patients with diffuse gastritis a tumor with scirrhous growth type may be wrongly considered as physiological RP uptake. And vice versa, local uptake of ^{18}F -FDG in the stomach wall, which is observed in most cases in the fundus of the stomach may be interpreted as a malignant lesion (Eary and Krohn 2000; Kubota et al. 1992; Stahl et al. 2001).

According to Valk et al. (2006), the rate of RP uptake in the stomach wall may be a reliable prognostic criterion of the disease. For example, if the standardized uptake value (SUV) is higher than 4.0, 2-year survivability is 51%, if the SUV is below 4.0 it is 81% ($p < 0.05$).

7.3.1.2 N Category

^{18}F -FDG PET sensitivity in diagnosing regional metastases is not high at 22%. At the same time its specificity may be 97%. The main causes of false-negative results are the small dimensions (less than 5 mm) of the affected lymph nodes due to small

Fig. 7.1 MDCT Multidetector CT (a) and ^{18}F -FDG PET (b) data for a patient with cancer of the gastric fundus



quantity of tumor substrate and of their image merging with contours of the primary formation (Bonenkamp et al. 1999; Lerut et al. 2000).

7.3.1.3 M Category

^{18}F -FDG PET in diagnosing distant metastases in SC is a highly informative method. First of all, it is due to the possibility of assessing a whole-body image within a single examination. Performing whole-body PET permits the detection of additional foci in 22–23% of SC patients. According to some data, PET is the most informative method of radio-visualization in diagnosing metastatic foci above 1 cm in the liver (Yoshioka et al. 2003). Meanwhile, the sensitivity of the method in detecting canceromatosis of the peritoneum and pleura is not high; it ranges within 21–23%. Apparently, it is due to the small size of implantation foci (less than 2–4 mm), which

are thus outside the limits of the resolving capacity of PET (Cook 2001; Roukos 1999; Roukos and Kappas 2002).

7.3.1.4 Treatment Efficiency Evaluation

^{18}F -FDG PET has high diagnostic accuracy in restaging SC during the postoperative period and in 37–42% of cases permits the visualization of additional signs of progression of the disease that are undetected by US and CT. In addition, metabolic disturbances are as a rule detected 2–3 weeks earlier than clinical-laboratory changes. The diagnostic accuracy of PET in detecting local relapse of the disease is still not completely studied. The main reason for that is high uptake of RP in the area of anastomosis or in the gastric stump conditioned by reparative changes. However, observing time intervals between implementation of PET and surgical treatment permits in many cases the avoidance of false-positive results (Czech et al. 2000; Hartgrink et al. 2000; Potter et al. 2002).

The use of PET for assessing tumor sensitivity to polychemotherapy is of much practical importance. The criterion of sensitivity of malignant cells to treatment is SUV dynamics assessed before and after therapy. A significant decrease in SUV after treatment correlates to the degree of medical pathomorphism (Couper et al. 1998).

So, ^{18}F -FDG PET is no doubt only an additional method of radiodiagnosis of SC, which shows its highest efficiency in staging, restaging and early assessment of the efficiency of therapy. At the same time, the use of this method for screening in case SC is suspected should be considered as premature.

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Presently colorectal cancer (CRC) is one of the most prevalent of oncological diseases. In 2003, 45,020 cases of CRC were detected in the Russian Federation (Merabishvili 2006). However, stages I-II of the disease were detected in only 22.8% of patients. In the remaining cases, signs of stages III and IV of tumor process were revealed. Consequently, within 1 year of tumor detection, lethality reached 32.3% and radical treatment was given to only 41.3% of patients (Shalimov et al. 2000).

Growth in number of CLC cases is influenced by the following factors: the nature of food (high-caloric food with prevalence of animal fats, proteins and refined carbohydrates-sugars); sedentary life leading to obesity, especially after the age of 50; hypotonia and atonia of the intestine at elderly age, accompanied by constipations; presence of endogenous carcinogens (indole, skatole, guanidine, metabolites of steroid hormones) in the intestinal contents; chronic traumatism of the mucous membrane of the large intestine in areas of physiologic curves; presence of precancerous diseases (chronic nonspecific and granulomatous colites, diverticulites and diverticuloses, polipous lesions).

Pathognomonic signs of colorectal cancer do not exist. The small-sized tumor as a rule does not manifest itself. As the malignant neoplasm grows, general symptoms of intestinal malfunction appear.

The main clinical forms of cancer of the colon include toxic-anemic, electrolytic, dyspeptic, obturative, pseudoinflammatory and tumorous (atypical) cancers. In case of colorectal cancer, the most frequent (and most often late) symptoms are bleeding, pain in the area of the perineum, functional bowel disorders (change in rhythm of defecation, form of faeces, diarrhea, constipation, fecal and gas incontinence).

8.1 Pathologic Anatomy and Mechanisms of Metastases

Malignant neoplasm is most often situated in the sigmoid colon and blind gut. In 1–3% of cases the lesion can have a multifocal character. The main ways of dissemination of the tumor process in CRC are via the lymphogenous, hematogenous

and implantation routes. The hematogenous and implantation mechanisms of metastasis in cancers of the colon and rectum do not have significant differences. On the contrary, lymphogenous metastasis of the large intestine has its own specific features.

Stages of Lymphogenous Metastasis of Cancer of the Colon

- Stage I – lesion of epicolic or paracolic lymph nodes
- Stage II – lesion of intermediate or mesenteric lymph nodes
- Stage III – lesion of paraaortic lymph nodes in the area of the root of mesocolon

As is known, lymph is accumulated in the lymphatic cistern situated at the level S1–2 and flows through the thoracic duct into the venous system in the area of the left venous angle, at the confluence of the subclavian and inner jugular veins, thus conditioning metastatic lesion of lymph nodes of the left supraclavicular (Virchow's metastasis).

Lymphogenous metastasis in rectal cancer depends entirely on the localization of the primary pathologic formation.

Characteristics of Lymphogenous Metastasis of Cancer of the Rectum

- In the case of supra-ampullary location of the tumor, its dissemination to lymph nodes occurs upwards along the superior rectal artery and from the root of inferior mesenteric vessels with involvement of retroperitoneal lymph collectors, most often paraaortic.
- In the case of infra-ampullary location of the tumor, pararectal lymph nodes are affected, situated along the middle and inferior rectal arteries. During further dissemination of tumor process lymph nodes of the hypogastric area are involved.
- Cancer of the anal section of the rectum is characterized by metastatic lesion of lymph nodes situated along inferior rectal arteries and of those of the hypogastric and inguinofemoral areas.

8.2 Methods of Diagnosis

The main methods of diagnosis of cancer of the large intestine are digital investigation of the rectum, procto(sigmoido)scopy, fibrocolonoscopy with target biopsy and irrigoscopy with “double” contrast. Radiological examination permits determination of the precise location of the malignant neoplasm, its size, relations with adjacent anatomic structures, and depth of lesion of the intestinal wall. Diagnostic accuracy of irrigoscopy is defined as 85–94%. Using transabdominal ultrasound (US) for detecting colorectal cancer is possible, but the detected signs are most often nonspecific. It is due to presence of gas in the intestine, which checks the passage of ultrasound waves. At the same time, it is the ratio of gas/tissue in the area of tumor, and not the extension of lesion, that is crucial in visualizing primary formations in the large intestine. This means that pathologic formation will be detected provided that the ratio of gas/tissue in the intestine changes in favor of the tissue, which is possible only in case of obstructing tumors.

The use of computed tomography (CT) for diagnosing malignant neoplasms of the large intestine is efficient only in late stages of the disease (T3 and T4). Consequently, using CT in CRC patients is suitable for determining tumor infiltration of surrounding anatomic structures and detecting signs of generalization of the malignant process. The main advantage of the method is its high resolving capacity (2–4 mm) and consequently possible visualization of small metastatic foci, including those in the liver. However, in case of subcapsular or subdiaphragmatic location of metastases, false-negative results may be obtained.

The diagnostic accuracy of CT in detecting secondary changes in the liver is in the range of 84–97% (Satsukevich 2003), the sensitivity reaches 80–90% with a specificity of 99% (Kinkel et al. 2002).

8.3 Staging

Clinical staging of the tumor process in cancers of the colon and rectum is implemented according to the international classification by the TNM system, which reflects three obligatory components: size and depth of invasion of the primary tumor, metastasis to regional and juxtaregional lymph nodes, and metastasis to distant organs (Edge 2010).

8.3.1 PET Diagnosis

8.3.1.1 Assessment by T Category

The diagnostic accuracy of positron emission tomography (PET) in detecting malignant neoplasms of the large intestine depends, as a rule, on the size of the primary tumor. So, sensitivity of the method in diagnosis of the late stages of the disease (T3–T4) may reach 92%. However, in the initial stages of tumor process this index does not exceed 56–64% (Cohade et al. 2003; Delbeke 1999; Meta et al. 2001). The widest spread causes of false-negative results are small size of pathologic formation and hypometabolism of ^{18}F -fluorodeoxyglucose (^{18}F -FDG) in malignant neoplasms of some morphologic kinds. For example, one should treat with caution negative ^{18}F -FDG PET results in highly differentiated and mucinous adenocarcinomas. In these histological forms of tumors ^{18}F -FDG PET sensitivity does not exceed 58% (Berger et al. 2000 and Abdel-Nabi et al. 1998).

Specificity of the method in diagnosis of colorectal cancer is relatively low and ranges within 66–71%. High uptake of radiopharmaceutical (RP) having a focal character may be observed in the area of benign villous polyps and in the projection of hemorrhoid boluses of the rectum. However, the most frequent cause of false-positive results is the physiologic uptake of RP in the intestinal wall due to its peristalsis. In these cases, the technique of delayed scanning of the region of interest can be used for determining the nature of detected changes. In case of physiologic uptake of RP in the intestinal wall in the delayed phase of the examination, the focus either will change its position because of intestinal peristalsis or will completely disappear.

So it is clear that ^{18}F -FDG PET cannot be the method of choice in differential diagnosis of solid masses of the large intestine and should be used only as an additional means.

8.3.1.2 Assessment by N Category

Since surgical treatment is obligatory in any stage of CRC and is implemented in order to prevent intestinal obstruction, hemorrhage and perforation, dissemination assessment according to the N category, at first sight is not essential. However, the volume of resection, radicalism of surgical intervention, prognosis and adequacy of treatment in CRC patients entirely depend on correct staging of the disease, including that using the N category.

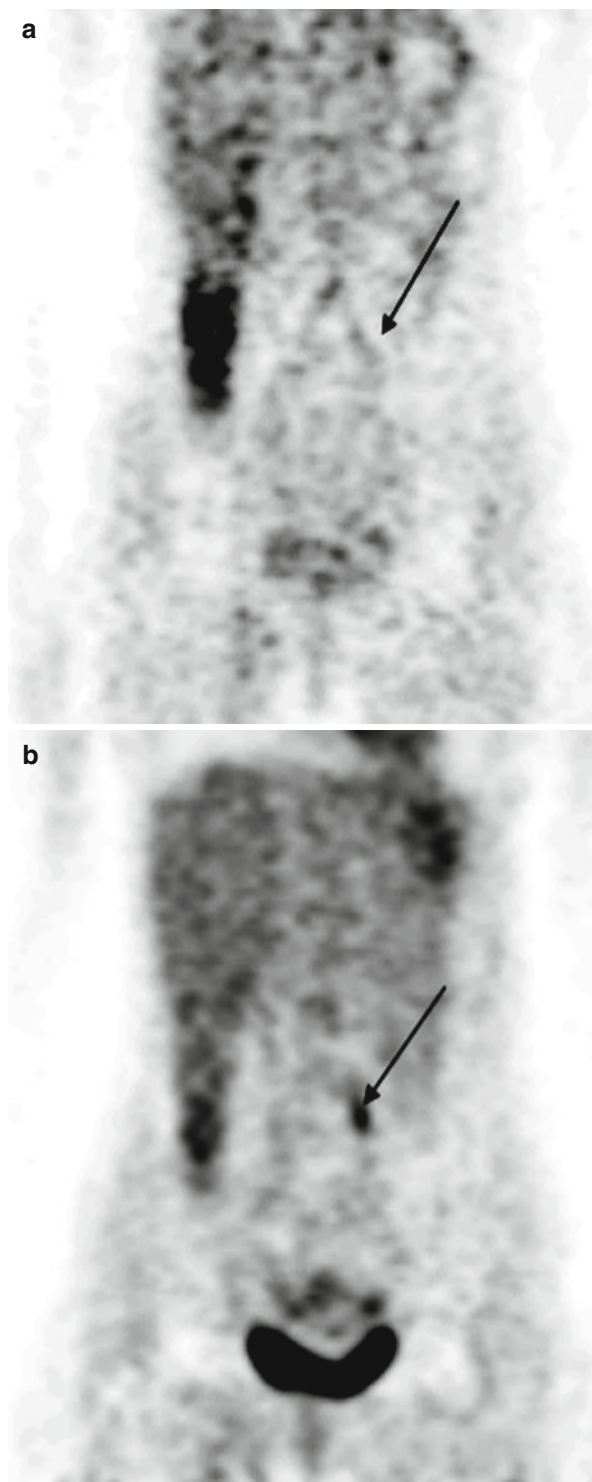
The role of ^{18}F -FDG PET in assessment of the state of lymph nodes in CRC patients is ambiguous and its information value thoroughly depends on the anatomic situation of the lymph node. For example, paracolic, mesenteric, proper mesenteric and pararectal lymph nodes, which are usually the first to be affected, are far from being always detected by means of PET. This is mainly due to small quantity of tumor cells in the affected lymph node, in consequence of which it is only insignificantly enlarged (less than 5 mm). Besides, regional lymph nodes are always situated near the primary formation and do not merge into conglomerates, which also makes their assessment considerably difficult. The sensitivity of PET in the diagnosis of metastatic lesion of the first-order lymph nodes does not exceed 29%, its specificity reaches 96% and is a reliable predictor of the degree of malignancy of the tumor (Kantorova et al. 2003). Using PET/CT and a nodal diameter cutoff value of 10mm sensitivity and specificity reaches around 30% and 95% respectively (Tsunoda et al. 2008).

When lymph correctors of the retroperitoneal space and lymph nodes of the inguinofoveal and iliac areas are involved in the tumor process, ^{18}F -FDG PET sensitivity reaches 93% and its specificity is 89% (Heriot et al. 1998). However, when implementing topical diagnosis of foci in these anatomic regions, difficulties may arise. The most frequent problem is local asymmetric uptake of RP in the projection of the retroperitoneal space. This can be observed both in case of physiologic uptake of RP in the ureter and in case of solitary lesion of a lymph node. In this situation, using delayed phase scan together with forced diuresis is obligatory. The focus of non-neoplastic character will not be visualized in repeated scanning of the region of interest as a consequence of the excretion of radioactive urine from the ureter (Fig. 8.1).

8.3.1.3 Assessment by M Category

^{18}F -FDG PET is a high-informative method of visualization in the diagnosis of distant metastases in patients with colorectal cancer. Whole-body examination permits restaging of the disease in 23% of patients owing to detection of additional metastatic foci. The diagnostic accuracy of PET in detecting secondary changes in the lungs, liver and lymph nodes ranges within 88–96% (Delbeke et al. 1997; Flamen et al. 1999; Lai et al. 1996). Fernandez et al. (2004) compared the results of whole-body PET with CT data in CRC patients with solitary metastatic lesion of liver.

Fig. 8.1 ^{18}F -FDG PET results: standard scan (**a**) and delayed scan (**b**) in a patient with rectal cancer. (**a**) slightly increased FDG uptake in a retroperitoneal focus (*arrow*). (**b**) physiologic uptake in the left ureter (*arrow*), no more uptake in the former focus, indicating the non-tumorous character



Liver resection was planned for all the patients. However, in a portion of the patients extrahepatic metastases were detected, which was the reason to cancel surgical treatment and to administer chemotherapy instead. In this process, 3-year survivability was 77%. Meanwhile, as is known, the 3-year survivability of CRC patients with solitary metastatic lesion of the liver does not exceed 40%. In this context the authors think that additional use of PET in CRC patients during the preoperative period may permit improvement of survival rate by excluding inoperable patients from the observation group.

8.3.1.4 Treatment Efficiency Evaluation

The high accuracy of PET in identifying viable tumor tissue in the area of therapeutic manipulations is of considerable practical importance. For example, in cancer of the rectum the most frequent problems are posed by differential diagnosis of post-operative or post-radiation fibrosis and local relapse of the disease in the presacral area. Absence of pathological uptake of ^{18}F -FDG in the area of surgical intervention or field of irradiation is a convincing sign of sclerotic alterations. Uptake of the RP in this area should be considered as indicating local relapse (Fig. 8.2). Meanwhile,

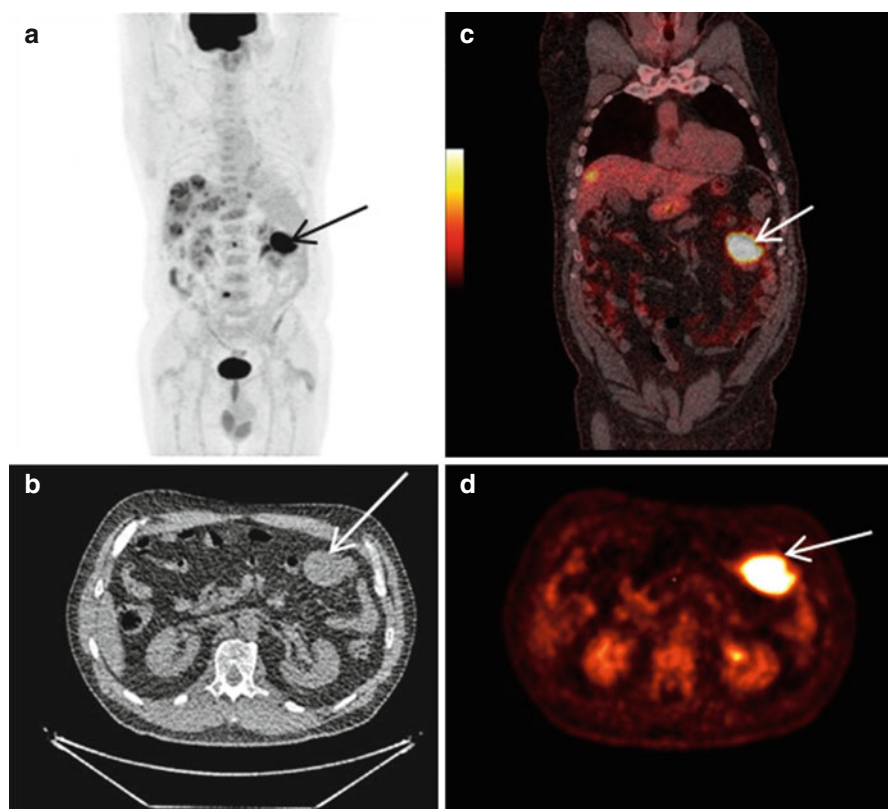


Fig. 8.2 ^{18}F -FDG PET (a, d), CT (b) and PET/CT (c) of a patient with recurrent colorectal cancer. Post-therapeutically staging. Metastases are detected in descending colon (arrow) and liver parenchyma

in case of the traditional examination algorithm (US, CT, MRI) used in this category of patients, reiterated implementation of different radiodiagnostic methods and assessment of results in dynamics are most often needed in order to determine the nature of changes. This, in turn, makes diagnosis take from 3 to 6 months in some patients with local relapse of cancer of the rectum (Meta et al. 2001).

¹⁸F-FDG PET is efficient for dynamic observation of CRC patients during the post-operative period. The results of PET examinations permit a change of therapeutic management in 20–30% of patients receiving polychemotherapy in the adjuvant regime. As far as detecting initial signs of disease progression is concerned, the sensitivity of PET considerably exceeds that of assessing carcinoembryonic antigen (CEA) level in blood serum, the former being 89% and the latter 75%. Besides, metabolic manifestations of disease relapse are detected by PET 2–3 weeks earlier than CEA increase. In addition, in solitary lesions the level of oncomarker may remain within normal values (Schiepers et al. 1995; Vitola et al. 1996; Ogunbiyi et al. 1997; Valk et al. 1999; Ruers et al. 2002).

Interesting results were obtained by Huebner et al. (2000), who compared standardized uptake values (SUVs) in metastatic foci of the liver in a patient with cancer of the colon before and after the operation. Increase in SUVs after operation was observed. The obtained results, in their opinion, confirm cytoreductive influence of primary large bowel mass on metastases in the liver.

Thus, PET is most informative in determining the process of dissemination of tumor, in dynamic observation of patients during the postoperative period and in differentiation of cicatricial adhesive alterations and viable tumor tissue in the area of therapeutic manipulations.

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The liver is the biggest parenchymatous organ, situated in the superior segment of the abdominal cavity under the diaphragm, mainly to the right. The liver takes an active part in all kinds of metabolism, digestion and blood circulation processes as well as in the fermentative, excretory and detoxification functions of the organism, as well as in many other functions. Functionally the structural unit of the liver is a lobule consisting of hepatocytes surrounding the central vein. Between particles of lobules there lie bile ducts which interflow into interlobular bile ducts beyond the lobules. The latter, when joined together, form the right and left hepatic ducts, which interflow beyond the liver into a common hepatic duct opening to the duodenum.

The blood supply of the liver occurs through the portal vein and hepatic artery; 70–80% of blood comes through the former and 20–30% through the latter. Blood outflow from the liver takes place through hepatic veins flowing into the inferior vena cava.

The liver consists of the right (and bigger) and left lobe, each of them being divided into four segments. This division is due to the portal vein branching into two big branches (for the right and left hepatic lobes); from each of them four second-order veins depart for each segment. The complexity of the anatomic structure of the liver and the diversity of its functions account for the difficulties in the diagnosis of pathological processes of the liver, especially tumor lesions.

9.1 Methods of Diagnosis

In spite of the introduction of high-technology methods of diagnosis (US, MDCT, MRI), it is only in 5–15% of cases that radical removal of the hepatic tumor is possible by the time of its detection. Up to 90% of liver cancer patients do not receive radical surgical treatment because of late diagnosis. This situation is no doubt associated with matters of general organization of oncological aid. However, there are still grave problems also in the diagnostic process. As is known, screening of liver

cancer is imperfect. Usually it includes analysis of clinical data, determining the content of alpha-fetoprotein in blood and US (Sakata et al. 2008). Experience shows that this information in many cases is insufficient since clinical data have a non-specific character and are not early, and the contents of alpha-fetoprotein (AFP) in blood virtually does not increase in some malignant tumors of the liver (Kehagias et al. 2000; Sakata et al. 2008).

US is an efficient method of diagnosis of liver cancer. However, results of examination are to a great extent determined by the operator's individual capacities and by the state of the apparatus. The last decade has been marked by the introduction of MDCT and MRI into clinical practice. Each of these methods develops intensively on account of improving hardware and software. Today, contrast-enhanced MDCT and CT arteriportography are used for the diagnosis of liver tumors. Besides standard MRI, dynamic contrast-enhanced MRI (DCMRI), MRI cholangiopancreatography, MRI venoportography, MR spectroscopy, etc. are also implemented. These methods have a high resolving capacity. As a rule they permit the detection of even slight structural changes in the liver. However, experience shows that in a number of situations diagnosis of liver cancer with the help of MDCT and MRI involves difficulties, especially when a tumor lesion accompanies cirrhosis. In such cases it is virtually impossible to distinguish a small tumor from nodes of hyperplasia. It should be noted that the use of contrast-enhanced CT and CT arteriportography is accompanied by a significant number of false-positive conclusions conditioned by changes in liver structure in cases of perfusion disturbances and fatty degeneration. In such cases, decisive information for differential diagnosis can be obtained by means of positron emission tomography (PET).

Liver tumors originate from hepatocytes, epithelium of bile ducts and mesenchymal tissue. The widest-spread histological classifications of malignant and benign liver tumors are shown in Tables 9.1 and 9.2 (Podymova 1998).

Table 9.1 WHO histological classification of tumors of the liver and intrahepatic bile ducts

Histological group of tumors	Histological type of tumors
Epithelial tumors	Malignant
	Hepatocellular carcinoma (liver cell carcinoma)
	Intrahepatic cholangiocarcinoma (peripheral bile duct carcinoma)
	Bile duct cystadenocarcinoma
	Combined hepatocellular and cholangiocarcinoma
	Hepatoblastoma
	Undifferentiated carcinoma
	Benign
	Hepatocellular adenoma (liver cell adenoma)
	Focal nodular hyperplasia
	Intrahepatic bile duct adenoma
	Intrahepatic bile duct cystadenoma
	Biliary papillomatosis

Table 9.1 (continued)

Histological group of tumors	Histological type of tumors
Non-epithelial tumors	Malignant Epithelioid hemangioendothelioma Angiosarcoma Embryonal sarcoma (undifferentiated sarcoma) Rhabdomyosarcoma Benign Angiomyolipoma Lymphangioma and lymphangiomatosis Hemangioma Infantile hemangioendothelioma
Miscellaneous tumors	Solitary fibrous tumor Teratoma Yolk sac tumor (endodermal sinus tumor) Carcinosarcoma Kaposi sarcoma Rhabdoid tumor Others
Hemopoietic and lymphoid tumors	
Secondary tumors	
Epithelial abnormalities	Liver cell dysplasia (liver cell change) Large cell type (large cell change) Small cell type (small cell change) Dysplastic nodules (adenomatous hyperplasia) Low-grade High-grade (atypical adenomatous hyperplasia) Bile duct abnormalities Hyperplasia (bile duct epithelium and peribiliary glands) Dysplasia (bile duct epithelium and peribiliary glands) Intraepithelial carcinoma (carcinoma in situ)
Miscellaneous lesions	Mesenchymal hamartoma Nodular transformation (nodular regenerative hyperplasia) Inflammatory pseudotumor

Table 9.2 Classification of benign liver tumors

Histological group of tumors	Histological type of tumors
Benign tumors	
(a) Tumors originating from the stromal and vascular elements	Hemangioma (cavernoma and true gemanoma), lymphangioma, fibroma, lipoma
(b) Tumors originating from epithelioid tissue	Adenoma
Non-parasitic cysts	Retention cystadenoma, dermoid cysts
Pseudocyst formations	Inflammatory and posttraumatic mesenchymal hamartoma, biliary hamartoma, congenital biliary cysts, focal nodular hyperplasia, compensatory lobar hyperplasia, etc.
Tumor-like formations	

According to Podymova S.D.

9.1.1 Epidemiology and Clinical Picture of Liver Tumors

9.1.1.1 Malignant Tumors

In recent decades the incidence of primary liver cancer has significantly increased. According to Weiss (1978), 20 years ago the frequency of primary liver cancer constituted 0–8% of all the pathomorphological studies and 3% of all the malignant tumors. Presently it constitutes 2–3% and 11% respectively (Podymova 1998). The mean primary liver cancer frequency in Russia is currently 6.2 per 100,000 of the population. There are regions where the values are much higher: in the basins of the Irtysh and Ob they constitute 22.5–15.5 per 100,000, cholangiocellular cancer being more often observed there. The development of cholangiocarcinoma is stimulated by parasitic diseases and helminthiases (amebiasis, schistosomiasis, opisthorchiasis and others). The risk of the disease in persons suffering from ulcerative colitis is higher by 10% than in the general population. Cirrhoses do not predispose to the development of cholangiocarcinoma. However, secondary biliary cirrhosis may develop due to tumor obstruction of bile ducts. On the whole it is hepatocellular cancer (HCC) that prevails among primary malignant liver tumors (80% of all primary liver cancers). In 60–80% of patients the development of hepatocellular cancer is associated with persistence of the viruses of hepatitis A and B. In 80–90% of these patients tumors accompany cirrhosis. Men develop the disease four- to ten-times more frequently than women. Among predisposing factors of hepatocellular cancer there are uncontrolled consumption of alcohol and other regular intoxications leading to cirrhosis.

Metastatic lesion of the liver is observed 20-times more frequently than primary liver tumors. According to different authors, from 77% to 90% of liver metastases are multifocal. Isolated lesion of one of the lobes of the liver (more frequently the right one) is observed in 10–30% of cases. Most often it is tumors of the large intestine (50–75%), pancreas (45–70%), mammary gland (10–60%), cholecyst and extrahepatic bile ducts (50–60%), stomach (20–50%) and lungs (10–40%) that metastasize to the liver. Some rarer localizations of primary tumors metastasizing to the liver are the esophagus, ovary, skin melanoma, prostate and kidneys (Prokop and Galansky 2003).

The predisposing factors of metastatic lesion of the liver are its double blood supply, a developed net of vessels of the microcircular channel, fenestrated basal membrane of sinusoids favoring the penetration of tumor cells and stimulation of tumor growth by local humoral factors.

9.1.1.2 Benign Tumors

The most frequent benign liver tumor is hemangioma. According to data obtained by autopsies, the frequency of this tumor ranges from 1% to 7%. Clinical examinations show that it is observed in 2–4% of adults. The main cause of development of liver hemangioma is considered to be associated with taking oral hormonal contraceptives. On the other hand, the dysembryoplastic theory seems to be fairly well-grounded, according to which liver hemangioma occurs in consequence of abnormal development of vessels in the phase of dysembryogenesis (Granov and Polysalov 1999). The second most frequent benign liver tumor is focal nodular hyperplasia. It is observed in patients

aged 20–50 and is four- to ten-times more frequent in women. Focal nodular hyperplasia is often detected accidentally during routine diagnostic examinations. It has been established that occurrence of this disease does not depend on taking oral contraceptives.

Hepatocellular *adenoma* is a rare form of benign tumor; one of its causes being taking oral contraceptives and androgen steroids.

The clinical picture of the indicated benign neoplasms of the liver does not as a rule permit the right diagnosis to be made without using methods of radiological diagnosis. When the dimensions of the tumor exceed 3–4 cm or there are hemorrhages to the tumor with its subsequent necrosis, abdominal pains are possible; in the rest of cases, asymptomatic disease course usually takes place.

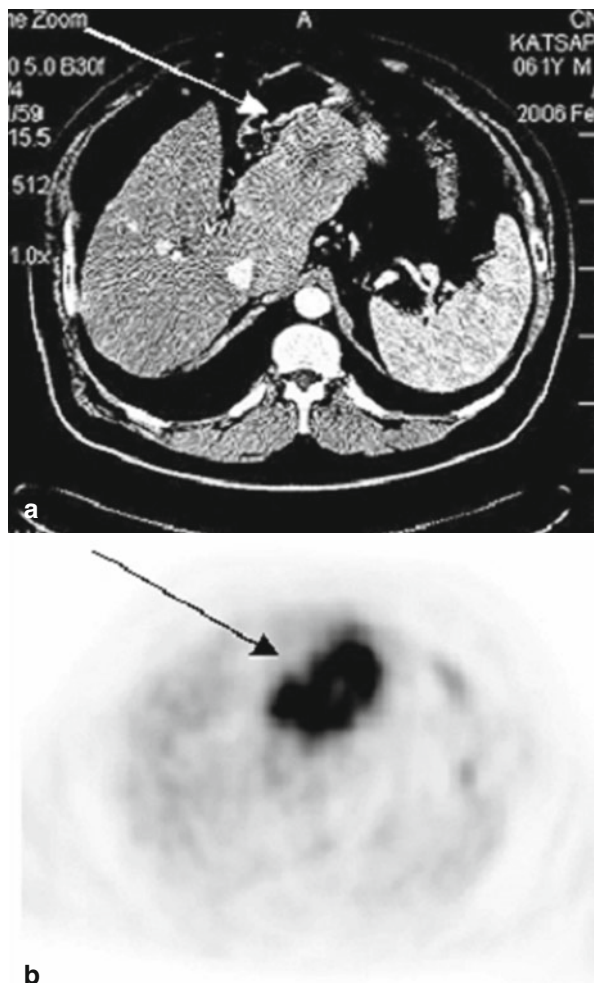
9.1.2 PET in Liver Tumors

9.1.2.1 ^{18}F FDG PET

^{18}F -Fluorodeoxyglucose (^{18}F -FDG PET) is an important and needful additional method of (Shin et al. 2006, Son et al. 2002 and Verhoef 2002) visualization and differential diagnosis of benign and malignant liver formations. The examination is implemented by the whole-body method with usual patient preparation. The main criterion of a malignant process when using ^{18}F -FDG PET, as in malignant tumors of other localizations, is high radiopharmaceutical (RP) uptake, usually having a focal character (Rohren et al. 2004; Ho 2004). Foci of pathologic ^{18}F -FDG uptake in the projection of liver space-occupying lesions of malignant nature have different dimensions, form and structure. Often several foci join into one tumor conglomerate (Kinkel et al. 2002). However, there are no pathognomonic PET signs obtained by only visual analysis that would permit differentiation between primary liver cancer and metastatic changes.

In the medical literature, the capacities of ^{18}F -FDG PET in diagnosis of hepatocellular cancer are widely covered. It has been established that highly differentiated hepatocellular cancer cells have glycolysis characteristics similar to those of normal hepatocytes. High excretion of glucose by the cell is accounted for by high contents of the phosphatase enzyme (Jong et al. 2005). As a consequence, in PE studies of some patients there is no pathological ^{18}F -FDG uptake characteristic for malignant tumors. However, in case of low differentiation of hepatocellular cancer, high RP uptake is observed in tumor tissue on account of its high metabolic activity. Maximum standardized uptake values (SUVs) in this histological variant of HCC, according to different authors make up from 3.7 ± 0.7 to 8.1 ± 1.3 (Fig. 9.1). For the indicated reasons ^{18}F -FDG PET permits the detection of only 50–70% of hepatocellular cancers, usually with low and moderate degrees of differentiation (Delbeke and Pinson 2003; Wudel et al. 2003). Meanwhile, this method has high sensitivity (90–100%), as for other malignant liver tumors. For example, in the diagnosis of cholangiocellular cancer high information value of ^{18}F -FDG PET has been reported, from 80% to 96% (Trojan et al. 1999; Jong et al. 2005), which is due to active RP uptake in the projection of cholangiocarcinoma. Kim et al. (2003) elicited in their research that PET is the most informative in nodular cholangiocarcinoma (sensitivity up to 96%). In the

Fig. 9.1 Hepatocellular cancer. **(a)** Contrast enhanced MDCT: heterogenous hepatic formation of mixed vascularization. **(b)** ^{18}F -FDG PET: pathologic FDG uptake in the tumor



case of the infiltrative form of the disease, the capacities of the method are limited. False positive results may be obtained in patients with acute cholangitis accompanying primary sclerosing cholangitis. ^{18}F -FDG PET permits the visualization of both peripheral cholangiocarcinomas and tumors situated in the porta of the liver (Klatskin tumors) (Jarnagin and Winston 2005). Many authors observe high information value of ^{18}F -FDG PET in metastatic lesion of the liver (Fig. 9.2) (Hustinx et al. 1998).

Comparative indices of the informative value of ^{18}F -FDG PET and MDCT in the diagnosis of metastatic lesion of the liver published in recent years are shown in Table 9.3.

In the case of metastatic lesion of the liver, according to Choi (2006), a particular advantage of PET is its capacity of detecting and assessing the state of

Fig. 9.2 Metastasis in the right lobe of the liver. **(a)** Contrast enhanced MDCT: hypodense formation in the right lobe of the liver. **(b)** ¹⁸F-FDG PET: pathologic -FDG uptake in the tumor

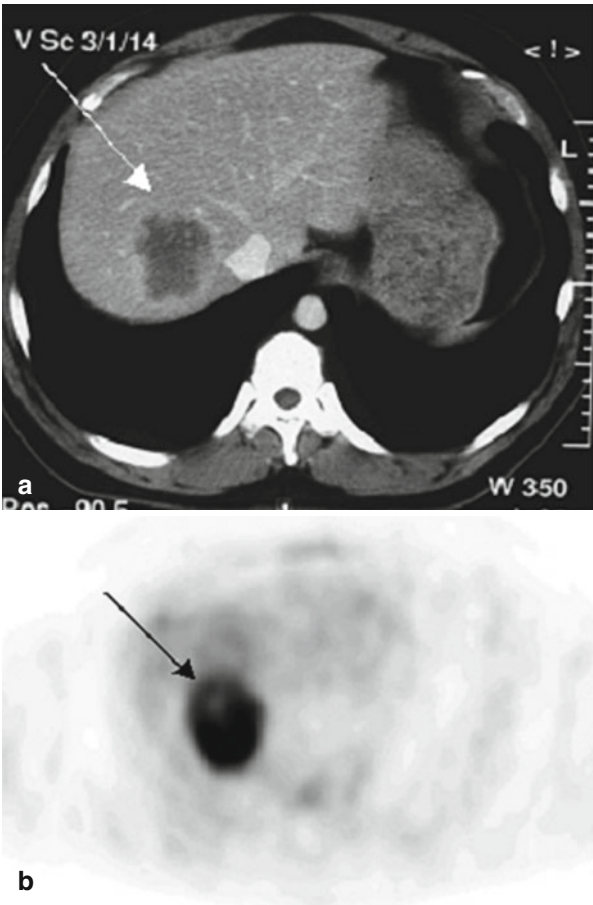
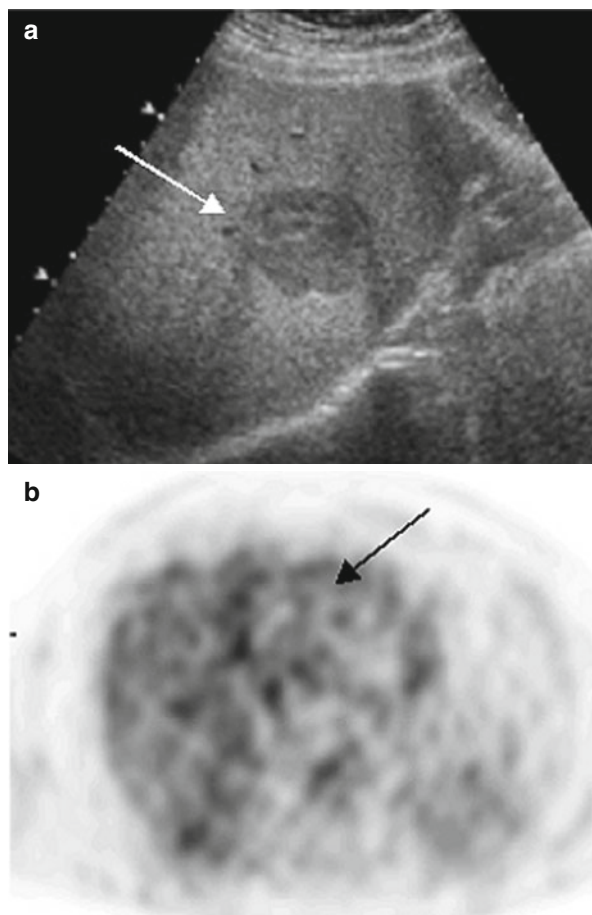


Table 9.3 Comparison of FDG PET and MDCT in diagnosis of metastatic liver lesions

Author	Year	FDG PET		MDCT	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Shiepers	1995	94	100	85	98
Delbeke	1997	91	95	81	60
Kinkel	1999	90	85	72	70
Valk	1999	95	100	84	95
Whiteford	2000	92	99	80	81

primary malignant tumor. Iwata et al. (2000) observed that in the differential diagnosis of benign and malignant formations the use of ¹⁸F-FDG PET in most cases permits the diagnostic tasks to be solved. This determines further patient management.

Fig. 9.3 Hemangioma of the right lobe of the liver. USD (a) formation of heterogenous structure in the liver with areas of hypo- and hyperechogenicity (arrow). ^{18}F -FDG data (b) absence of pathologic FDG uptake in the lesion (arrow)



At the same time, the absence of pathological RP uptake in the projection of the space-occupying lesion of the liver detected by means of other methods of radiological visualization in most cases (except for some types of HCC) is considered as a benign disease. In particular, absence of FDG uptake is observed in all the patients with hemangiomas, adenomas, foci of focal nodular hyperplasia and nodular fatty infiltration of the liver (Figs. 9.3 and 9.4). ^{18}F -FDG uptake in the projection of formations corresponds to its background value ($\text{SUV}_{\text{max}} = 1.10 \pm 0.08$) (Iwata et al. 2000; Kurtaran et al. 2000). Currently, the possibility of wide use of ^{18}F -FDG PET for treatment efficiency evaluation is under consideration. Such a study will permit the determination not only of structural tumor changes but also of cell transformation at the metabolic level (Fig. 9.5).

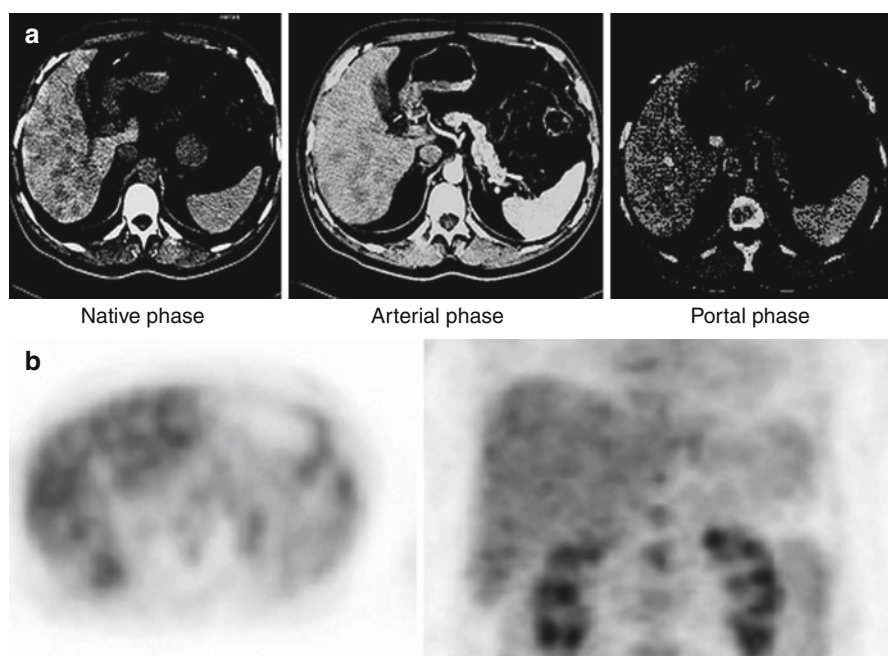
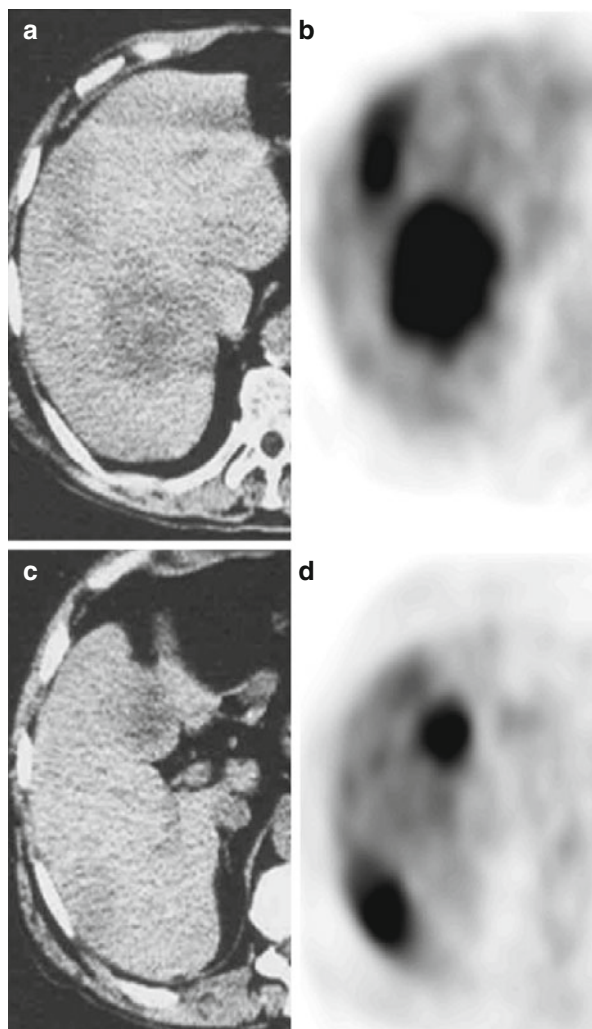


Fig. 9.4 Nodal fatty infiltration of the liver. Contrast enhanced MDCT (**a**) multiple hyperdense formations in the liver parenchyma. ^{18}F -FDG PET (**b**) physiologic FDG uptake in the lesions

Diagnostic criteria of using ^{18}F -FDG PET in assessing the efficiency of treating malignant liver tumors have been defined. Variants and criteria of the metabolic tumor response to treatment for ^{18}F -FDG PET are indicated in Table 9.4.

It is clear from Table 12 that complete metabolic tumor response to treatment is defined in terms of complete absence of ^{18}F -FDG uptake in the projection of its focal hyperfixation visualized before treatment (Fig. 9.6). Partial tumor response to treatment may be stated on the basis of persistent RP uptake in the projection of the formation but with the maximum SUV decreasing no less than by 25% (Fig. 9.7). In the case of a progressing malignant process, when using ^{18}F -FDG PET the typical characteristics include enlargement of the tumor and increase in SUV_{max} by more than 25% and/or appearance of new foci of RP uptake. Persistence of the focus of pathological RP uptake after treatment with change (increase or decrease) in SUV_{max} no more than by 25% in the absence of growth of the formation attests to the stabilization of the process. It should be noted that all PET results should be confirmed by data of other methods of radiological visualization.

Fig. 9.5 Cholangiocellular carcinoma. Heterogeneous hypodense formations in the liver (MDCT, **a, c**) with pathological ^{18}F -FDG uptake (PET, **b, d**) before the treatment. Absence (**f, h**) of pathologic ^{18}F -FDG uptake in projection of formations visualized (**e, g**) by Lipiodol CT after regional chemotherapy (3 courses of chemoembolization – doxorubicin, 5-FU, cisplatin)



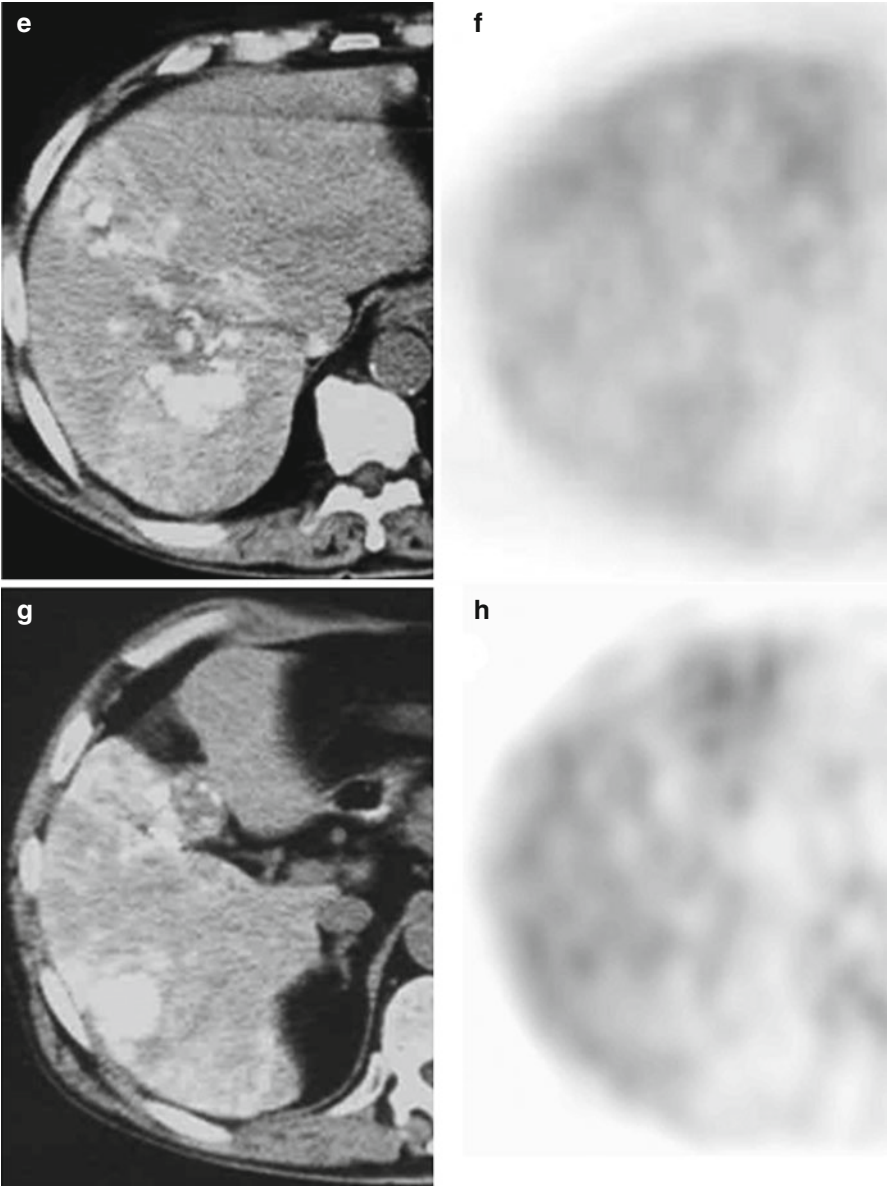


Fig. 9.5 (continued)

Table 9.4 EORTC response criteria (Wahl 2009)

CR	Complete resolution of ^{18}F -FDG uptake within tumor volume so that it was indistinguishable from surrounding normal tissue
PMR	Reduction of minimum of 15 % to up to 25 % in tumor ^{18}F -FDG SUV after one cycle of chemotherapy, and >25 % after more than one treatment cycle; reduction in extent of tumor ^{18}F -FDG uptake is not a requirement for PMR
SMD	Increase in tumor ^{18}F -FDG SUV <25 % or decrease of <15 % and no visible increase in extent of ^{18}F -FDG tumor uptake (20 % in longest dimension)
PMD	Increase in ^{18}F -FDG tumor SUV of >25 % within tumor region defined on baseline scan; visible increase in extent of ^{18}F -FDG tumor uptake (20 % in longest dimension); or appearance of new ^{18}F -FDG uptake in metastatic lesions

Fig. 9.6 Metastasis of colorectal carcinoma in the right lobe of the liver ^{18}F -FDG PET.
(a) Metabolically active lesion before treatment
(b) physiologic uptake after regional chemotherapy. Complete metabolic response

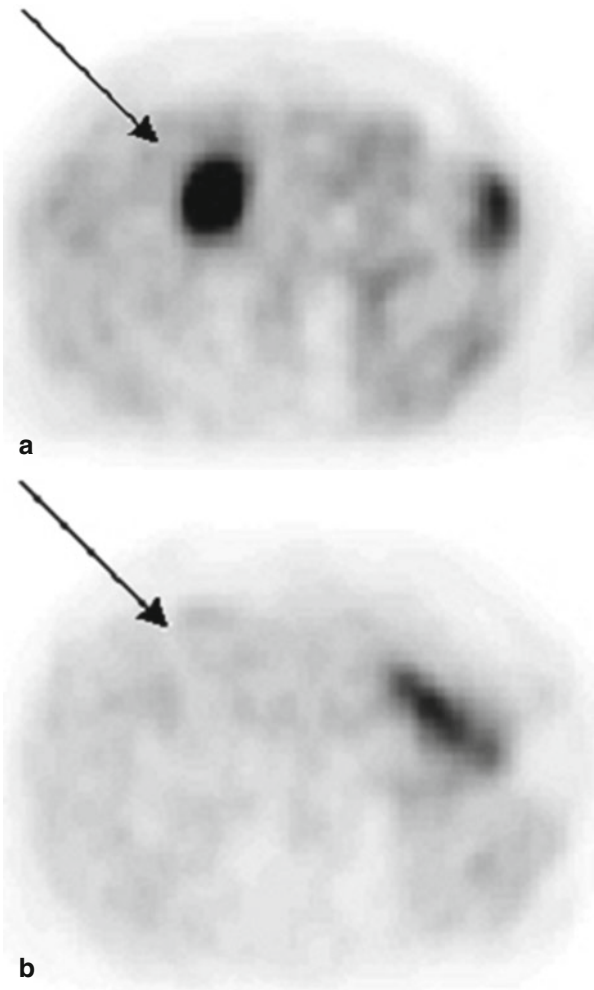
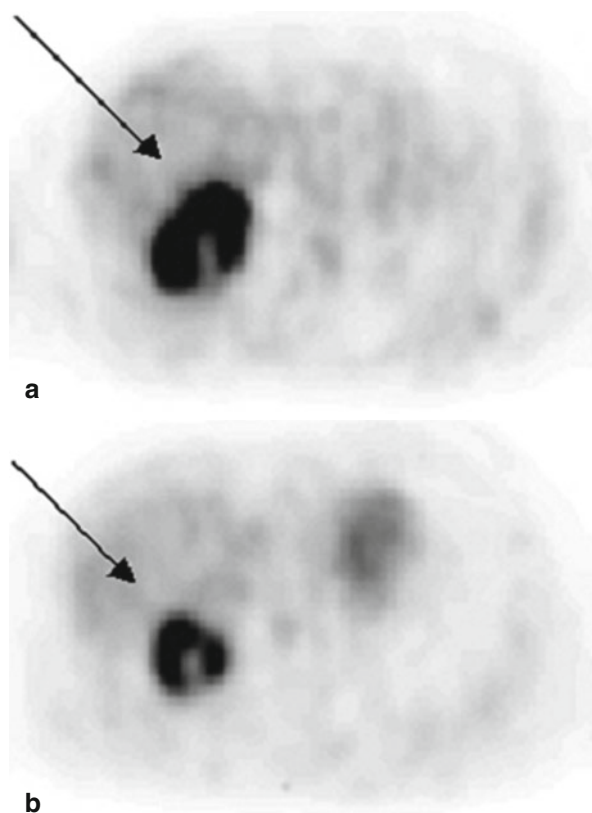


Fig. 9.7 ^{18}F -FDG PET before (a) and after (b) regional chemotherapy. Partial metabolic response



9.1.2.2 ^{11}C -Acetate PET

^{11}C -Acetate is considered to be the precursor of a number of biologically important substances, including amino acids. It ensures the highest accuracy in detecting some malignant tumors, such as meningioma, glioma, lymphoma and others (Dimitrakopoulou-Strauss 2003; Seltzer et al. 2004). At the same time, acetate permits assess of the metabolism in the myocardium. One of the advantages of this RP is the relatively brief time required for an examination (45 min after the injection). The half-life period of ^{11}C -acetate is 20 min. Currently ^{11}C -acetate is successfully used in detecting and differentially diagnosing malignant liver tumors. Examination is implemented 85–105 min after intravenous RP injection (i.e., 4–5 half-life periods) and consists of scanning the epigastric region of the patient, which is the area of the anatomic situation of the liver. PET results are assessed by means of quantitative analysis of RP uptake in the projection of the liver neoplasm. It has been observed that the sensitivity of the method in detecting HCC is 87.3%. For example, highly differentiated HCC are characterized by high uptake of this RP. The SUV_{max} is 7.32 ± 2.02 . In HCC with a low degree of differentiation as well as in cholangio-carcinomas and metastases of different primary tumors (cancers of the large

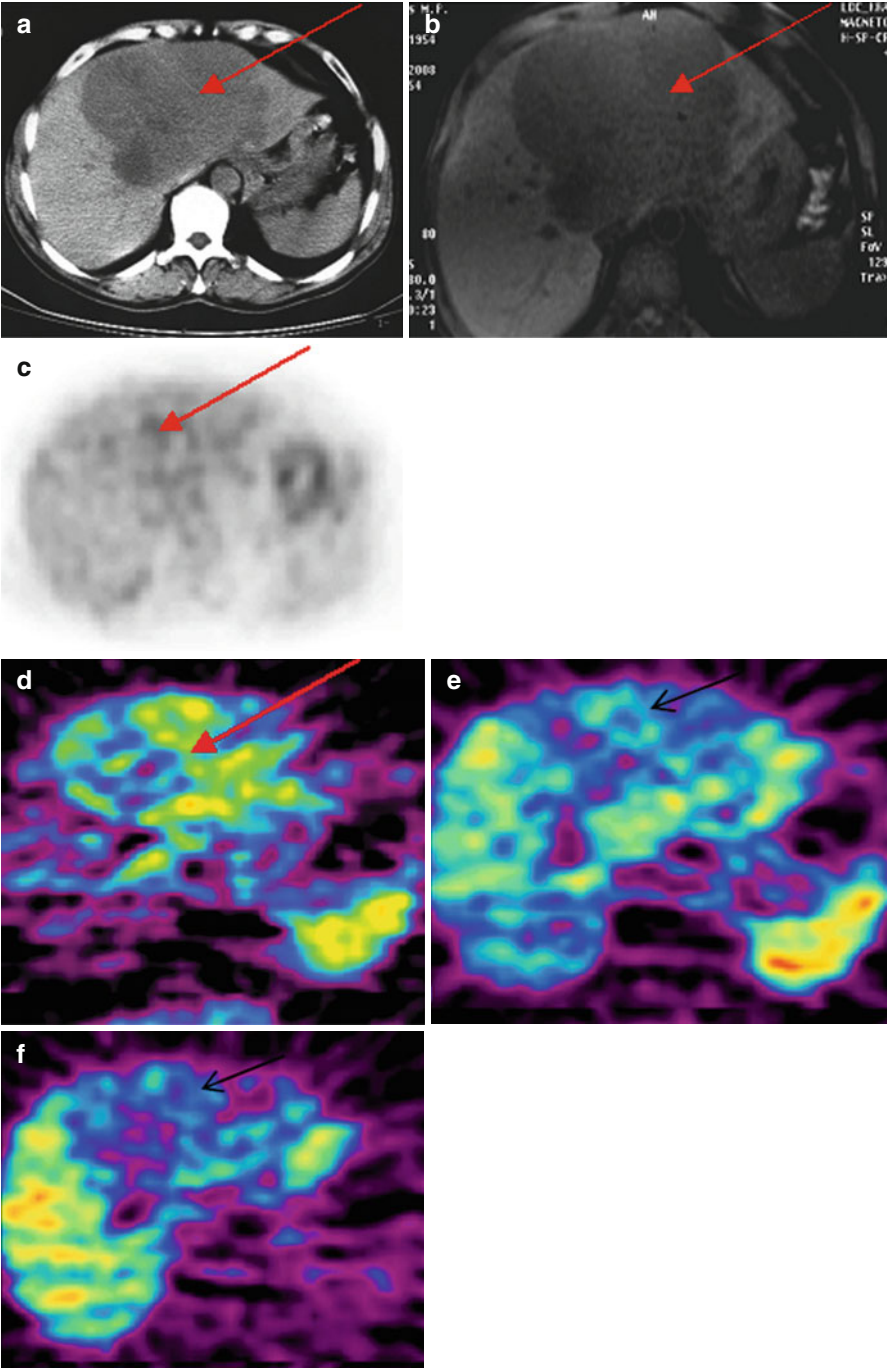
intestine, mammary gland, and lung), ^{11}C -acetate uptake is absent, which is an utterly important differential-diagnostic criterion (Ho et al. 2003; Delbeke and Pinson 2003). So, combined use of ^{18}F -FDG and ^{11}C -acetate significantly increases the capacity of PET in the differential diagnosis of liver neoplasms.

9.1.2.3 ^{13}N -Ammonia PET

^{13}N -Ammonia is the third most frequently used RP (after ^{18}F -FDG and ^{15}O -water). In diagnostic practice it is most frequently used in assessing myocardium perfusion. However, there are several studies devoted to the role of this RP in diagnosis of tumor lesion of the liver (Shibata et al. 1988). Examination is performed in order to determine the vascularization of malignant liver tumors. ^{13}N -Ammonia PET starts immediately after introducing 750 MBq and consists of scanning only the liver itself. The duration of this dynamic regime is 20 min. When assessing the data obtained, quantitative analysis of RP distribution both in the formation itself and in the surrounding parenchyma is done. Pathological uptake of ^{13}N -ammonia in the projection of the tumor in scans obtained during the first minutes of examination (2.5–5 min) is conditioned by high tumor vascularization. At the same time in presence of hypovascular masses ammonia hypofixation in tumor is observed during the entire examination. This is most distinctly imaged in the presence of an active RP uptake by the unchanged parenchyma of the liver during the last minutes of examination. HCC, in most cases (except for mixed variants), are characterized by high ^{13}N -ammonia uptake in the initial stages of scanning, which corresponds to the arterial contrast phase in CT and MRI, and is considered as tumor hypervascularity (Fig. 9.8). This is an additional criterion in the differential diagnosis of metastatic liver tumors, since most metastases are hypovascular.

Thus, PET is an efficient additional method of radiological diagnosis of liver tumors, permitting valuable information for the differential diagnosis of benign and malignant processes to be obtained in complex clinical situations. ^{18}F -FDG PET is particularly informative in cholangiocellular and metastatic cancers. Use of PET has proved to be especially efficient in studying tumor reactions to treatment. A relatively low sensitivity of ^{18}F -FDG PET in the case of HCC, associated with the characteristics of metabolism in this tumor, dictates the necessity of using alternative tumor seeking agents.

Fig. 9.8 Well-differentiated hypovascular hepatocellular carcinoma. Hypodense formation in the liver (a) on CT, hypointense (b) on MRI. Absence of radiopharmaceutical uptake on ^{18}F -FDG PET (c). Active uptake of ^{13}N -ammonia in the first minutes (d) and its subsequent quick washout (e and f)



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Epidemiological studies of recent years have registered a steadfast growth in the number of pancreatic cancer cases. In the Russian Federation this number grows by 1.2% annually, and the increment of pancreatic cancer cases for recent years has been 11%. The share of pancreatic cancer in oncological mortality makes up 5% (Aksel et al. 2001).

Smoking, excessive consumption of meat products and fat, use of alcohol in big doses and hard manual labor are the essential risk factors for pancreatic cancer. There are cases of occurrence of a malignant neoplasm with antecedent pancreatic diabetes. Consequently persons older than 50 years of age who have a sudden development of diabetes, especially without hereditary load, should be considered to belong to the group of risk. Primary chronic pancreatitis may be also a background disease for development of pancreatic cancer due to dysplastic, metaplastic and disregeneratory changes of epithelium of the pancreas (Kazyulin and Kucheryavyi 2005; Kubyshkin and Vishnevsky 2003).

The clinical picture of pancreatic cancer most often develops gradually. On average, 3–4 months pass between the start of clinical manifestations and diagnosis. Among the initial manifestations of pancreatic cancer there are discomfort in the upper part of the abdomen (sensation of heaviness and repletion, especially after meal), pain, loss of weight, lowering of the appetite and nausea. The most apparent symptom appearing in the late stages of the disease is obturative jaundice, whose frequency and intensity are influenced by tumor localization and size, as well as by its relation to biliary ducts. In 70% of cases, jaundice is preceded by different symptoms caused by background diseases and complications of tumor growth. Therefore, several clinical forms of pancreatic cancer during the pre-jaundice period are distinguished: pancreatitis-like, diabetoid, cholangitic and gastritis-like. The duration of the period without jaundice is from 1 to 6 months. Tumor invasion to the duodenum is characterized by symptoms of gastroduodenal obstruction, intestinal hemorrhage and cholangitis (Maev 2004 and Putov 2008).

10.1 Pathologic Anatomy and Mechanisms of Metastases

Growth of malignant tumor of the pancreas occurs by way of cancer infiltration of the inter-tissue space and lymphatic sheets lying inside glandular lobules, as well as through connective-tissue spaces surrounding ducts, vessels and nerves of the pancreas. Its further expansion leads to the invasion of the capsule of the pancreas and to infiltration of retroperitoneal cellular tissue in which the portal vein and its affluxes are situated. Depending on the location of malignant neoplasm in the pancreas, it is accepted to distinguish cancer of the head, body and tail of the pancreas as well as diffuse or total lesion of the organ. The frequency of cancer of the head of the pancreas is 58–75%, that of the body of pancreas is 12–23% and that of the tail of the pancreas is 5–7%; the frequency of diffuse lesion being 1–6%. The dimensions of the tumor node range from several millimeters to 12–14 cm. Tumors of the head and tail of the pancreas are usually more massive than those of the corpus.

In 80–90% of cases it is adenocarcinoma in various degrees of differentiation that is the morphologic norm of ductal cancer of the pancreas. Rarer are planocellular, glandular-planocellular, anaplastic, giant-cell cancers and carcinosarcoma. Acinic-cell (parenchymatous) cancer microscopically belongs to alveolar tumors and occurs most often in the area of the body and tail of the pancreas.

Tumor dissemination in pancreatic cancer occurs in three ways: lymphogenous, hematogenous and by implantation. Tumor metastasis through lymph collectors takes place in several stages:

- Stage 1 – lesion of pancreatoduodenal lymph nodes
- Stage 2 – lesion of retropyloric and hepatoduodenal lymph nodes
- Stage 3 – lesion of celiac and superior mesenteric lymph nodes
- Stage 4 – lesion of retroperitoneal (most frequently paraaortal) lymph nodes

In the cases of hematogenous and implantation ways of tumor dissemination, distant metastases are observed in the liver, lungs, kidneys, bone system and peritoneum.

10.2 Methods of Diagnosis

Presently US is the first stage of the diagnostic algorithm in examining patients with solid pancreatic masses. The diagnostic accuracy of the method in detecting pancreatic cancer ranges within large limits and varies from 48% to 86%. The sensitivity of US in the diagnosis of invasion of great blood vessels corresponded to 43% and in determining tumor resectability was 30.5% (Arablinsky et al. 1992; Kotlyarov 1999; Casadet et al. 2002). The appearance of multi-layer spiral CT has considerably increased the possibilities for radiodiagnosis. When combined with intravenous or intraarterial (CT arteriportography) contrast, the accuracy of the method may reach 82–93% (Bronstein et al. 2004).

MRI is one of the most efficient radiological methods of examining the duodenal area. Use of dynamic contrast-enhanced MRI permits the performance in many cases of the differential diagnosis of pseudotumorous pancreatitis and tumor lesion of the pancreas. The introduction of MR aortoportography and venoportography has

considerably increased the information value of MR examinations, as well as MR cholangiopancreatography, which permits the visualization of biliary tracts and the duct of Wirsung. Complex application of all the mentioned MR techniques permits an increase in the diagnostic accuracy of the method in pancreatic cancer of up to 88–97% (Amthauer et al. 2002).

Much importance in the diagnosis of pancreatic cancer is still attached to endoscopic X-ray cholangiopancreatography. When implementing it, one can carry out intake of pancreatic juice, and obtain material by brush-biopsy for cytological study with rather high efficiency. However, changes in pancreaticograms in patients with chronic pancreatitis are detected in 72–76% and in pancreatic cancer patients only in 24% of cases; if tumor is localized in the uncus they are detected in no more than 10–15% of patients. In 10% of cases, pancreaticograms in the event of pancreatic cancer resemble those for chronic pancreatitis (Revyakin et al. 1996; Schofl and Haefner 2003).

It should be noted that despite the wide spectrum of radiological methods of examination, the problem of differential diagnosis of pancreatic cancer and pseudo-tumorous pancreatitis cannot be considered as resolved. In many cases the similarity of radiological symptoms in both diseases does not permit to differentiate between tumor lesion of the pancreas and benign focal hyperplasia, which finally results in rather low specificity of the obtained data. At the same time, the adequacy of treatment, prognosis and life quality of patients with solid masses of the pancreas directly depend on timely and accurate diagnosis.

Another important problem is the diagnosis of metastatic lesion of lymph nodes in pancreatic cancer. In US and CT examinations, the enlargement of lymph nodes is the most frequent (and in many cases the only) sign of their tumor affection. Meanwhile, changes in size of a lymph node do not always mark it as a malignant lesion. Cases are known when the diameter of a lymph node in pancreatic cancer corresponded to 40 mm according to US and CT. However, in a morphological study of biopsy material, signs of reactive hyperplasia were detected. The main cause of enlargement of a lymph node in pancreatic cancer lies in marked inflammatory changes in glandular tissue, which usually accompany a malignant process.

10.3 Staging

Clinical staging of the tumor process in pancreatic cancer is done according to the international TNM classification, which reflects three obligatory components: the size of the primary tumor, metastasis to regional lymph nodes and metastasis to distant organs.

10.3.1 PET Diagnosis

10.3.1.1 T Category

The role of PET in assessment of T category in pancreatic cancer is very important. It is due primarily to the high sensitivity of PET in the diagnosis of pancreatic

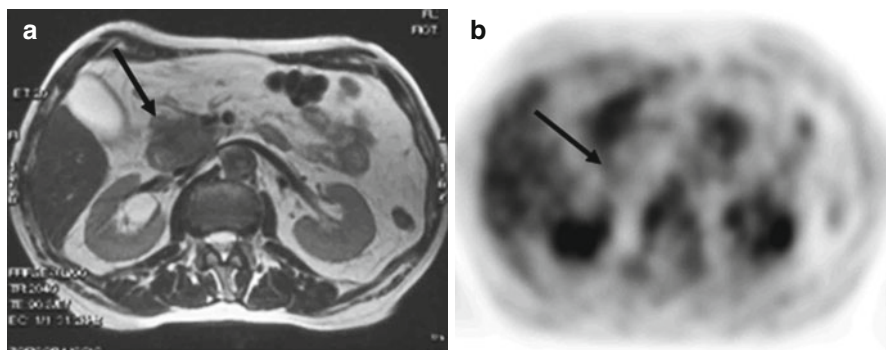


Fig. 10.1 MRI (a) with chronic pseudotumorous pancreatitis in remission without ¹⁸F-FDG uptake on PET (b)

cancer (94%), which considerably exceeds that of CT and MRI (71% and 88%, respectively). False-negative results in PET examination may be induced by high tumor differentiation and by dimensions of pathologic formation below 7 mm. The reduction or absence of radiopharmaceutical (RP) uptake in the tumor may be observed in the presence of a high level of endogenous glucose in blood plasma. Therefore, performing ¹⁸F-FDG PET in patients with pancreatic diabetes and consequent high blood glucose levels (higher than 11 mmol/mL) is not advisable (Clemens et al. 1995; Bagnenko et al. 2000; Ca van Kouwen 2003; Granov et al. 2003).

Presently there is no unanimity as for the specificity of PET data. For example, the specificity of PET in the differential diagnosis of pancreatic cancer and chronic pseudotumorous pancreatitis in the remission stage approaches to 98%. Absence of pathological uptake of RP is a reliable differential-diagnostic criterion in discriminating benign focal hyperplasia of the pancreas from a malignant process (Fig. 10.1). At the same time, high RP uptake in the area of inflammation induced by granulocytic and macrophage activity and observed in patients with acute chronic pseudotumorous pancreatitis exacerbation may lead to false-positive results (Berberat et al. 1999; Paros et al. 2002).

In order to increase PET specificity, some authors suggest implementing examinations in the dynamic regime with subsequent assessment of histograms reflecting the dynamics of RP uptake in tumor and in normal tissue (Nakamoto et al. 2003; Voth et al. 2003; Zimny and Schumpelick 2002). In doing so, high RP uptake is observed in malignant neoplasm during the first minutes of examination and continuous RP uptake is observed until the end of scanning. Fairly low RP uptake is observed in intact tissues during the first minutes of examination, and its slight decrease is observed towards the end of scanning (Fig. 10.2).

At present, the technique of two-phase scanning with diagnostic positioning 120 and 240 min after the introduction of RP has been developed. A significant increase

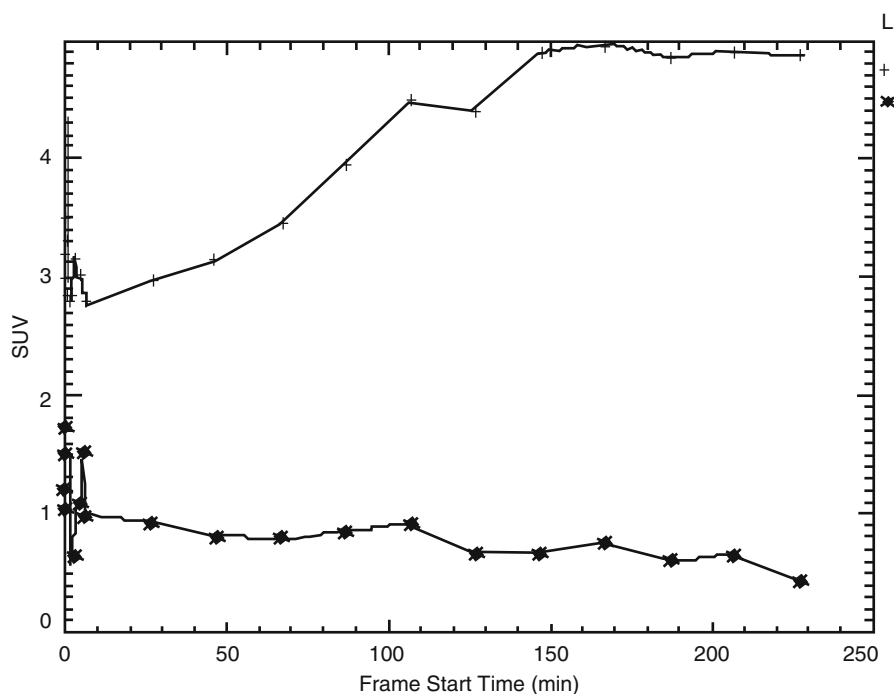


Fig. 10.2 ^{18}F -FDG uptake in a tumor (*upper curve*) and in intact tissues (*lower curve*) in dynamic PET

in standardized uptake values (SUVs) in delayed scanning in patients with pancreatic cancer and a slight decrease in these values in acute chronic pseudotumorous pancreatitis are the differential-diagnostic criterion in discriminating inflammatory changes and malignant lesion (Fig. 10.3).

10.3.1.2 N Category

The efficacy of ^{18}F -FDG PET in the diagnosis of metastatic lesion of regional lymph nodes depends on their anatomic situation. PET sensitivity in detecting secondary changes in lymph nodes of the pancreatoduodenal area does not exceed 34% (Fig. 10.4). The main causes of false-negative results are the proximity of location of first-order lymph collectors to the primary formation (especially in cancer of the head of the pancreas) and, in consequence, their image merging with anatomic contours of the tumor, and small size of lymph nodes (less than 5 mm). Meanwhile the diagnostic accuracy of PET in detecting metastatic lesion of celiac, superior mesenteric and paraaortal lymph nodes makes up 92%. The unquestionable advantage of PET is the possibility of assessing the state of normal-size lymph nodes (Maisey et al. 2000).

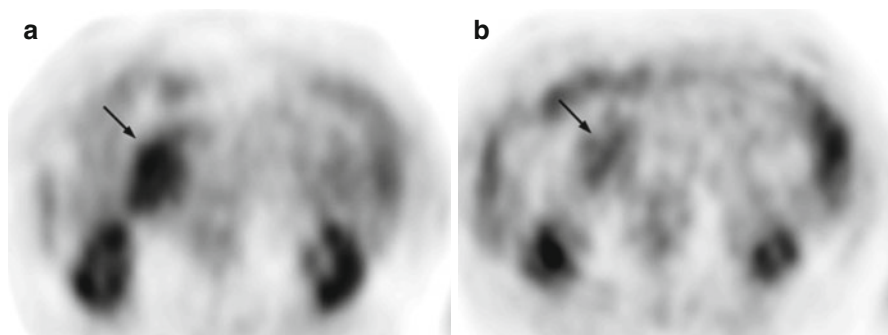
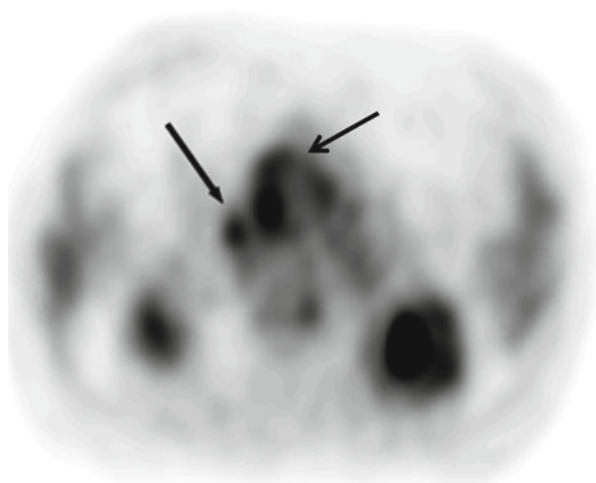


Fig. 10.3 Patient with acute condition of chronic pseudotumorous pancreatitis. Two-phase ^{18}F -FDG PET after 120 minutes (**a**) and 240 (**b**) minutes. (**a**) Pathologic FDG uptake is visualized in the mass lesion (*arrow*). (**b**) FDG upake in the mass lesion decreases more than 25% (*arrow*)

Fig. 10.4 ^{18}F -FDG PET of patient with cancer of the head of pancreas with metastatic lesion of a regional lymph node (*arrows*)



10.3.1.3 M Category

The role of ^{18}F -FDG PET in the diagnosis of distant metastases is hard to overestimate. Whole-body PET image permits the detection of secondary changes practically in any anatomic region, which in most cases influences the choice of therapeutic tactics. The diagnostic accuracy of PET in detecting metastatic lesion of the liver and of lymph nodes of distant areas ranges within 89–94% (Berberat et al. 1999). When PET is used in patients with pancreatic cancer in the pre-operative stage with a potentially residual tumor of the pancreas, the disease can be restaged in 12–17% of cases due to detection of additional metastatic foci (Fig. 10.5).

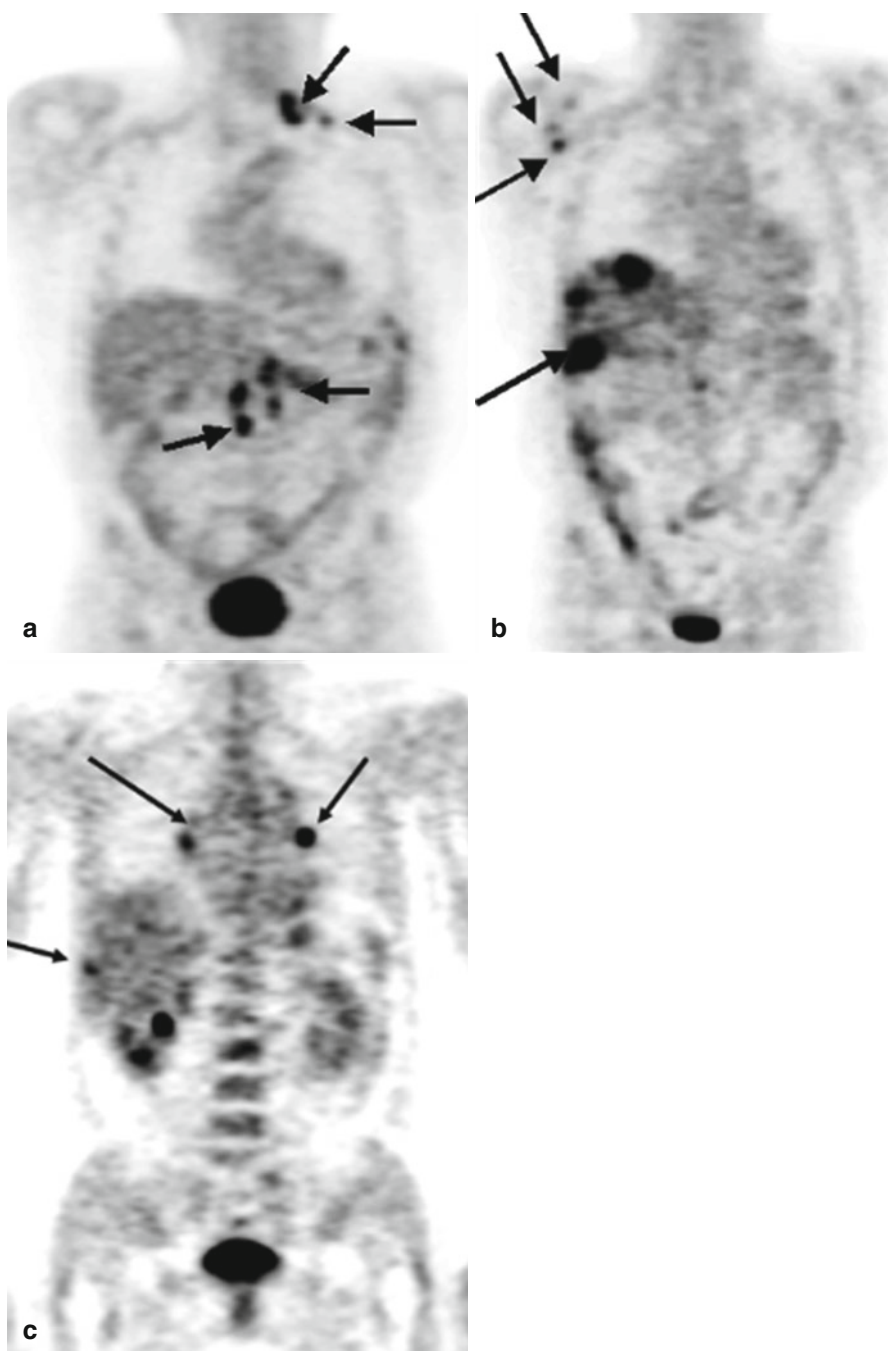
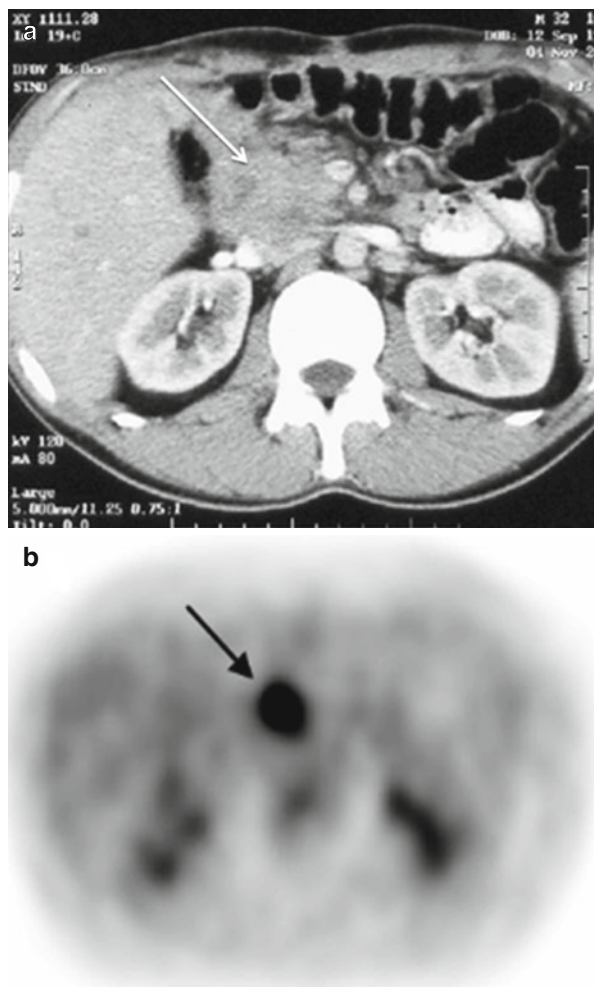


Fig. 10.5 Whole-body ^{18}F -FDG PET of three patients with pancreatic cancer. (a) metastatic lesions in left supraclavicular lymph nodes and paraaortic lymph nodes in the upper abdomen; (b) metastatic lesions in right internal axillary lymph nodes and in the liver; (c) bilateral metastatic lesions of mediastinal lymph nodes and in the liver

10.3.1.4 Pancreatic Cancer Treatment Efficiency Evaluation

The frequency of occurrence of local pancreatic cancer relapse half a year after radical surgical intervention reaches 50%. At the same time the early detection of continued tumor growth, even when using highly informative methods of radiological visualization (US, MDCT or MRI), still poses considerable difficulties. Laboratory diagnosis, in particular the determination of the level of oncomarkers in blood serum, also is little informative. Implementation of PET in pancreatic cancer patients in the post-operative period has much practical importance. The diagnostic accuracy of the method in detecting early signs of local relapse makes up 96% (Fig. 10.6).

Fig. 10.6 Local pancreatic cancer relapse (*arrows*) after pancreatoduodenal resection (**a**) early phase contrast enhanced MSCT (**b**) pathological ^{18}F -FDG uptake on PET



In this connection, whole-body examination in patients with a high level of onco-markers in blood serum during the postoperative period, and in the absence of signs of disease progression according to US, CT or MRI data, should be implemented once every 3 months.

10.3.1.5 Prognostic Value of ¹⁸F-FDG PET in Pancreatic Cancer

Some research results indicate a correlation between the intensity of metabolic processes in malignant neoplasms and disease prognosis (Maisey et al. 2000). At present, it is established that the level of RP uptake in a locally disseminated pancreatic tumor is considerably lower than in a malignant neoplasm in patients with distant metastases ($p=0.0032$). Further, the comparison of SUVs of tumor with the rates of factual and expected survivability in pancreatic cancer patients permitted discovery of the threshold value of SUV_{max} , relative to which survivability rates are different. For example, in patients with maximum SUVs greater than 6.8 life span is less than 9 months (Fig. 10.7).

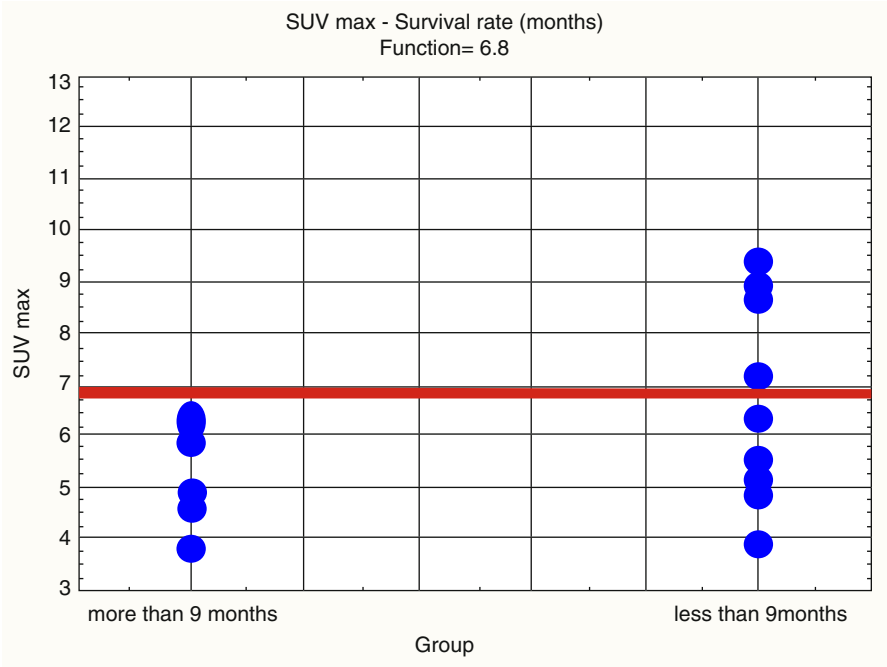


Fig. 10.7 Comparison of SUVs with regard to the expected life span of pancreatic cancer patients

It follows then, that ^{18}F -FDG PET is a highly informative method of radionuclide diagnosis of pancreatic cancer. It becomes possible by its use to differentiate within a single examination inflammatory changes and pancreatic cancer, to do staging and restaging of the disease in the post-operative period, and to detect with high diagnostic accuracy signs of local relapse of the tumor process.

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It is accepted to distinguish several forms of malignant kidney tumors, the most frequent ones (85%) being hypernephroma or renal cell carcinoma originating from the cells of the renal parenchyma. Kidney sarcoma or Wilms' tumor is observed exclusively in early childhood and is diagnosed in 90% of cases in children younger than 5 years old. Wilms' tumor forms almost a half of all malignant tumors in children. Cancer of the renal pelvis originates from the epithelium of the renal pelvis and makes up 7% of all kidney tumors.

Renal cell carcinoma is observed relatively rarely (about 3% of all malignant neoplasms in adults). The frequency of kidney cancer grows by roughly 2.5% annually. The individual risk depends on the age and presence of risk factor for the disease. The exact cause of kidney cancer is unknown; however, due to the results of numerous epidemiological studies some risk factors associated with this disease have been detected.

The incidence of renal cell carcinoma depends on age and achieves its peak by the age of 70 years. Men suffer from the disease twice as often as women do. Smoking is one of the most significant risk factors for development of different malignant neoplasms, including renal cell carcinoma. The risk of kidney tumor in smokers is twice as big as that in non-smokers. In case of abandonment of smoking the probability of developing the disease decreases. Most studies confirm the unfavorable impact of being overweight on the probability of developing kidney cancer. Body weight fluctuations and significant weight gain in adults are independent risk factors for this disease. The exact mechanism of the influence of obesity on the development of kidney tumor is not clear at present. Perhaps it is due to increase in concentration of endogenous estrogens and/or to biological activity of insulin-like growth factors. High risk of developing renal cell carcinoma is reported in persons occupied in the textile, rubber and caoutchouc, and paper industries or dealing with industrial dyes, petroleum and its derivatives, industrial poisons, and salts of heavy metals.

The risk of developing renal cell carcinoma jumps in persons with terminal-stage renal insufficiency in patients on long hemodialysis.

Genetic mutations increase the risk of developing kidney cancer. There is a high probability of kidney cancer in persons with von Hippel–Lindau syndrome. This

syndrome is based on the germinal mutation of the *VHL* gene situated in the chromosome locus 3p25. As a result, abnormal production of many growth factors is observed, in particular of those responsible for angiogenesis. Besides kidney tumors, neoplasms of the pancreas, adrenal glands and brain are observed in mutated *VHL* gene carriers.

Birt-Hogg-Dube syndrome is characterized not only by the occurrence of chromophobic renal cell carcinomas and oncocytomas but also by the presence of multiple tumors of hair follicles and bronchopulmonary cysts. Mutation of the *BHD* gene localized in the short arm of chromosome 17 is associated with this syndrome.

In patients with tuberous sclerosis, there are often cysts in the kidneys, liver and pancreas and the probability of developing kidney cancer is higher.

Kidney neoplasms in children represent 20–50% of the total number of tumors observed in childhood. Unfortunately, benign tumors are observed seldomly among kidney tumors in children, malignant kidney tumors in children being in 95%; they are called nephroblastomas or Wilms' tumors. Wilms' tumor has been called after the German surgeon Max Wilms (1867–1918), who first described this kidney tumor and established its histogenesis in his monography in 1899. Wilms' tumor is observed in children of different ages, most frequently from 2 to 5 years old. In 4–5% of cases, a bilateral lesion is observed. Nephroblastoma is very seldomly observed in adults; such patients make up 0.9% of all the kidney tumor patients.

The source of Wilms' tumor is associated with disturbance in the embryonic development of the fetus; this is attested by its frequent combination with congenital malformations. It has been established that mutations in the *WT1* gene not only lead to the development of Wilms' tumor but also manifest themselves by different anomalies of the urogenital organs, aniridia (congenital absence of the iris), congenital hemihypertrophy, Beckwith-Wiedemann syndrome. Besides detected disturbances in certain genes, an important role in developing nephroblastoma has been recently assigned to dysregulation of fetal mitogens, in particular to the elevated expression of the gene of insulin-like growth factor 2.

Cancer of the renal pelvis is a malignant kidney tumor originating from the transitional epithelium of the pelvis and accounting for about 7% of all kidney tumors. Depending on the histological structure, three forms of malignant epithelial neoplasms are distinguished: transitional cell carcinoma, papillary cancer and adenocarcinoma. Most neoplasms of the renal pelvis and ureter are represented by transitional cell carcinoma. This kind of tumor is often observed in patients with chronic pyelonephritis and sometimes accompanies leukoplakia of the pelvis. From the diagnostic and therapeutic points of view, a very important characteristic of papillary cancer of the pelvis is the fact that in 50% of patients with this disease a similar blastomatous process in the ureter or in the urinary bladder or in both is simultaneously observed. Consequently, simultaneous lesion of the renal pelvis, ureter and urinary bladder with papillary tumors is a typical phenomenon. Therefore, in case of suspicion of this kind of neoplasm it is necessary to examine the whole urinary tract.

The risk of developing cancer of the renal pelvis is several times higher in smokers compared with non-smokers. When smoking, concentration of intermediates of tryptophan metabolism increases, these intermediates having a structure similar to that of orthoaminophenol and are strong carcinogens.

It has been established that long presence of concrements in the renal pelvis increases risk of planocellular cancer of the renal pelvis; these concrements are carcinogens and induce hyperplasia of the urothelium.

The WHO classification is now the most complete and perfect; it has been drawn up by a working group of leading pathologists from different countries and adopted as a result of a consensus achieved in discussing the problem at the Lyon conference in 2002. The WHO classification groups tumors according to tissues to which they belong and to degrees of their malignancy.

In the present chapter devoted to kidney cancer, we thought it suitable to include only a fragment of the WHO histological classification concerning malignant kidney tumors.

11.1 WHO Histological Classification of Malignant Kidney Tumors

Renal Cell Tumors

Nephroblastic Tumors

Mesenchymal Tumors

Neuroendocrine Tumors

Tumors of the Hemopoietic and Lymphoid Tissues

Germinogenic Tumors

Choriocarcinoma

Metastatic Tumors

The most frequent is clear cell kidney cancer (60–85%), while the rarest histological type of renal cell cancer is collecting duct tumor (1–2%).

It should be noted that the presented classification embraces only neoplasms of the renal parenchyma and does not include the pelvicalyceal system. The practical suitability of dividing malignant kidney tumors into those of the renal parenchyma and those of the renal pelvis does not provoke doubts since they differ from each other in histological structure, ways of metastasizing and methods of treatment.

The morphological characteristic of the tumor process includes also gradation of degrees of malignancy:

Gx – the degree of malignancy cannot be assessed

G1 – high-differentiated tumor

G2 – moderate-differentiated tumor

G3 – low-differentiated tumor

G4 – undifferentiated tumor

The classification of renal cell cancer follows the TNM Classification.

11.2 Clinical presentation and metastases

Kidney cancer metastasizes in the hematogenic and lymphogenic ways. In approximately 30–50% of patients, metachronous metastases appear in different spaces of time after nephrectomy. Metastases of renal cell cancer are most often localized in the lungs (76% of cases), lymph nodes (64%), bones (43%), liver (41%), ipsilateral (19%) and contralateral (11.5%) adrenal glands, contralateral kidney (25%) and brain (11.2%).

Solitary metastases or metastatic lesion of one sole organ take place in 8–11% of cases. Wilms' tumor metastasizes to the liver, perinephric lymph nodes and to the lungs.

When speaking about the course of metastatic disease in renal cell cancer, one cannot but mention cases of spontaneous regression and stabilization. Spontaneous regression is observed in 0.4–0.8% of kidney cancer patients. This regards in most cases regression of lung metastases. Disease stabilization, defined as absence of growth and of new metastases, is observed in 20–30% of patients. Stabilization of primary tumor in patients with kidney cancer without metastases is observed with the same frequency.

The clinical picture of kidney cancer is composed of the typical triad of symptoms: pain syndrome, hematuria and solid mass in the retroperitoneal space detected by palpation. However, all of these symptoms are observed only in the advanced stage of the disease, while in early stages usually one or two of them are observed. Sometimes malignant kidney tumors are accompanied by a steadfast rise of temperature. In some cases there is a dilatation of the veins of the spermatic cord on the side of tumor, not disappearing when in the horizontal position. This symptom appears when tumor invades the venous vessels.

Kidney tumors in children do not manifest themselves with the indicated triad of symptoms. They are often revealed accidentally during bathing or during an examination for another disease. Clinical manifestations take place mainly in late stages. Among local symptoms, it is hematuria and pain that are most often observed.

Arterial hypertension is an inconstant symptom, provoked by compression of segmental renal arteries, occlusion of the ureter or high rennin secretion.

Syndrome of compression of the postcava: edemas of the lower limbs, varicocele, dilatation of hypodermic veins of the abdomen, deep vein thrombosis in the lower limbs developing in 50% of patients in the presence of tumor thrombosis of the postcava or of its compression by tumor and enlarged lymph nodes.

Kidney cancer is distinguished by paraneoplastic syndromes conditioned by production of different biologically active substances by tumor tissues: erythropoietin, rennin, parathormone, insulin, glucagon, chorionic gonadotropin. In consequence, arterial hypertension, erythrocytosis, hypercalcaemia, hyperthermia, etc. may be observed in patients. These symptoms may be the only manifestation of the disease and should alert the physician as for possible tumor lesion of the kidneys. Besides that, amyloidosis is a rare form of the paraneoplastic syndrome.

Symptoms conditioned by metastatic lesion of different organs occupy a particular place in the clinical picture of kidney cancer. The first symptom of metastases to the lungs is dry cough and haemoptysis. Secondary lesion of the skeleton

manifests itself with pain syndrome and development of pathologic fractures. Brain lesion is accompanied by the rapid occurrence and growth of neurological symptoms.

General symptoms of tumor intoxication (anemia, high erythrocyte sedimentation rate, appetite loss, loss of weight, weakness) are signs of late stages of the disease.

11.3 Methods of Diagnosis

The objectives of modern methods of radiologic visualization in patients with malignant neoplasms consist of assessing the dimensions of the tumor focus, degree of tumor invasion of the pelvicalyceal system, vessels and pararenal cellular tissue, as well as in determining the dissemination of metastatic lesion.

US has a high resolving capacity. In the presence of tumor the contours of the kidney are deformed, echo signal is inhomogeneous because of areas of necrosis, hemorrhages and abrupt absorption of sound by tumor. US of the kidneys has the primary importance in the first stage of examination.

The radiologic signs of cancer of the kidney include an increase in size and changes in contours of the kidney, deformation and filling defects of the calycean-pelvic system. In the renal angiograms the signs of tumor are the dilatation of the lumen of the main renal artery, chaotic pathologic vascularization in tumor mass, premature segmental nephrogram, and enhancement of tumor stain. In interpretation of excretory urograms, attention should be paid to deformed contours of the calycean-pelvic system, disorganization of the typical arrangement of calices, amputation of calices, expanded distance from the edge of the calices to the external contour of the kidney, filling defect in the pelvis with uneven and indistinct contours, and deviation of the upper section of the ureter.

CT permits the detection of a solid kidney mass with diameter less than 2 cm, assessment of its location relative to the kidney segment, its surface and vessels of the renal porta and pelvicalyceal system, determination of the depth of invasion into the parenchyma of the kidney, the structure of tumor, possible infiltration of the paranephric cellular tissue, presence of thrombus in the renal vein and postcava, tumor invasion into the abdominal cavity, as well as presence of regional and distant metastases. The sensitivity of MDCT in detecting the primary focus is 100%, its specificity is 95%; for retroperitoneal lymph nodes they are 95% and 45% respectively (Schoder and Larson 2004).

Kidney cancer should be differentiated from solitary kidney cyst, polycystosis, hydronephrosis, abscess and carbuncle of the kidney, tuberculosis of the kidney, or, more seldom, from tumor of the adrenal gland and retroperitoneal tissue.

11.4 PET Diagnosis

Published data on the efficacy of ^{18}F -FDG PET in the diagnosis of kidney cancer are few and ambiguous. Some authors observe high sensitivity and specificity of ^{18}F -FDG PET in detecting the primary focus and local relapse in renal cell cancer

Fig. 11.1 ^{18}F -FDG PET of a patient with renal cell carcinoma, T4N0M0. Pathological uptake in the lower pole of the right kidney (arrow), physiological uptake in the myocardium and excretion by urinary system of both kidneys



(Bachor et al. 1996; Hoh et al. 1996; Ramdave et al. 2001) (Fig. 11.1). High ^{18}F -FDG uptake in primary tumor node in renal cell cancer was first established by Wahl (1991) during experimental research. However, PET examinations of patients with renal cell cancer permitted in some cases the detection of the same degree of intensity of ^{18}F -FDG uptake in a tumor node as in the unchanged parenchyma of the kidney. Similar results were obtained by Shreve (1998) in examining a representative group of patients with renal cell cancer (68 persons). The level of metabolic activity in the tumor node was insignificantly higher than that in the parenchyma of the kidney, especially when PET examination was done 1–2 h after ^{18}F -FDG injection. The most important problem for the interpretation of renal FDG uptake is still the physiological renal elimination of FDG. If there is no significant dysmorphism of the kidney out of tumorous lesion we can not discriminate tumor metabolism and urine activity for example in the pelvicalyceal system. The image fusion in PET/CT improves the results but does not solve the problem.

Ramdave et al. (2001) compared the results of ^{18}F -FDG PET with those of CT in diagnosis of renal cell cancer. The diagnostic accuracy of ^{18}F -FDG PET was the same as that of CT and made up 94%. Aide et al. (2003) detected a rather modest sensitivity but a high specificity of ^{18}F -FDG PET in renal cell cancer – 47% and 80% respectively. The comparative analysis of the sensitivity of ^{18}F -FDG PET (60%) and that of intravenous contrast CT (92%) presented in the work of Kang (2004) has convincingly demonstrated the advantage of the latter in

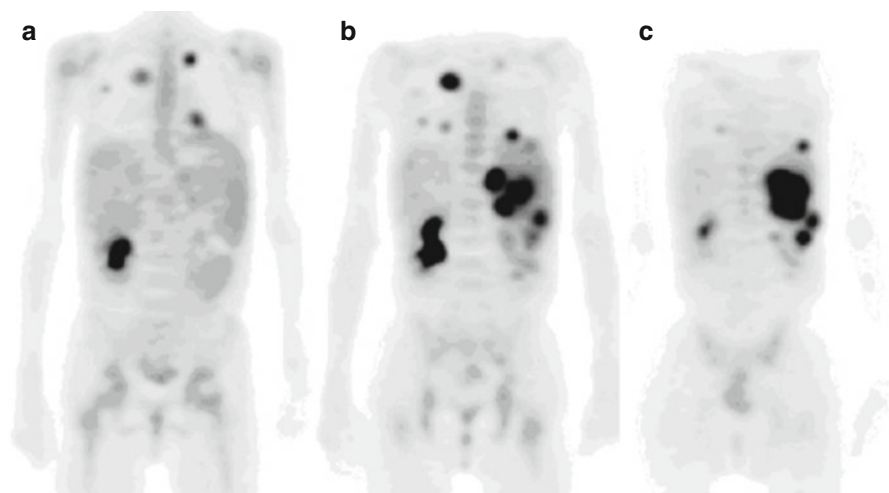


Fig. 11.2 Patient with Wilms's tumor, pT4N2M1, state after left-side nephrectomy, with pathological uptake ^{18}F -FDG showing local recurrence of the tumor, multiple metastases in spleen and both lungs in various slices of PET (a, b, c)

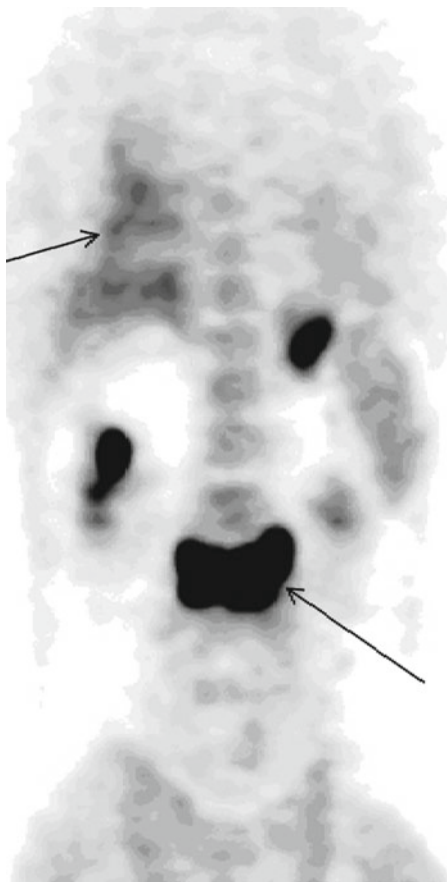
identifying the primary tumor focus. In the study of Bachor et al. (1996) the sensitivity of ^{18}F -FDG PET made up 77%. False-negative results were observed in six cases. In order to find the sources of false-negative ^{18}F -FDG PET results, Wahl (1997) compared PET data with the morphologic and histochemical tumor structures. High ^{18}F -FDG uptake was observed only in low-differentiated tumors with a high degree of expression of GLUT1 receptors, which are membrane glucose transporters.

It should be noted that ^{18}F -FDG PET exceeds in specificity other radiologic methods in detecting metastases (Kocher et al. 1994; Levine 1995; Poggi et al. 2001; Safaei et al. 2002) (Figs. 11.2 and 11.3). A higher sensitivity and specificity of ^{18}F -FDG PET were established as regards regional and distant metastases: the sensitivity and specificity of the method, according to different authors, ranged from 63% to 77% and from 75% to 100% respectively. True positive results were observed only when the size of lymph nodes was big (more than 1.7 cm), whereas in tumor-affected lymph nodes with sizes from 0.7 to 1.4 cm background ^{18}F -FDG uptake was observed in most cases. However, CT is more informative in diagnosis of metastatic lesion of the lungs.

Besides, an advantage of ^{18}F -FDG PET over osteoscintigraphy has been detected in the diagnosis of metastases to the bones (Seto et al. 2000). This field of diagnosis is perhaps the only point where ^{18}F -FDG PET has a leading position.

The sensitivity and specificity of the method in revealing osteolytic metastases are 77% and 100%, respectively.

Fig. 11.3 ^{18}F -FDG PET of a patient with renal cell carcinoma (upper pole of the right kidney) and metastatic lesions of the II lumbar vertebra and lower lobe of the right lung (arrows)



Thus, ^{18}F -FDG PET has a low efficacy in the diagnosis of the primary tumor site in patients with kidney cancer; however, it can be successfully used for assessing the dissemination of metastatic process.

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Ovarian cancer is the fifth most frequent cause of death from oncologic diseases in women. Ovarian cancer is notable for unsatisfactory treatment outcomes due to the asymptomatic course of the disease and, in consequence, late diagnosis. This disease is characterized by rapid growth with subsequent spread to adjacent organs, dissemination through the organs of the small pelvis and abdominal cavity, and extensive lymphogenic and hematogenic metastasis. The probability of tumor recurrence in the third to fourth stages reaches 96% of cases within 6 months to 2 years after the end of primary treatment.

Ovarian cancer is observed mainly in women over 40 years old. Among the causes of developing the disease are: hereditary predisposition, continuous inflammatory processes in the uterine appendages or surgeries of benign tumors. Pregnancy decreases the risk of developing ovarian cancer, and infertility, on the contrary, increases the probability of its emergence. Environmental factors matter too.

Ovarian cancer classification is rather complex; it is based on numerous signs: dissemination, histological type, premorbid background, etc. Primary ovarian cancer originates from unchanged epithelial tissue. Secondary cancer develops in consequence of transformation of benign neoplasms. Metastatic cancer results from dissemination of malignant tumors of other localizations (endometrial, mammary or gastrointestinal cancers). Secondary ovarian cancer develops in consequence of malignization of cilio-epithelial cystomas, pseudomucinous cystomas, dermoid cysts, primary sex cord-stromal tumors, including granulosa cell tumors, androblastomas, thecomas.

On the basis of histological signs, three main groups of malignant ovarian tumors are distinguished: epithelial, germinogenic and stromal tumors. The overwhelming majority of malignant ovarian tumors are of the epithelial origin (from the integumentary epithelium of the ovary). They are divided into serous, mucinous, endometrioid, clear cell mesonephroid, Brenner tumors, mixed tumors of the epithelial origin, and undifferentiated tumors. Malignant growth characterizes also virilizing Leydig and Sertoli cell tumors and tumors of germinogenic origin: dysgerminomas, chorionepitheliomas, and immature teratomas. The most aggressive tumors are those of germinogenic origin, most of all chorionepitheliomas, the most rapid-growing and metastasizing tumors.

The FIGO system is a generally accepted classification reflecting stages of the disease. In the first stage, the tumor is confined to the ovary. The second stage is characterized by lesion of the ovaries and injury of their capsule. In the third stage, the tumor spreads through the peritoneum and there are lesions of the retroperitoneal and inguinal lymph nodes, of the surface of the liver and omentum. The fourth stage is characterized by the presence of remote metastases.

Ovarian cancer metastases through the peritoneal leafs, mainly with serous liquid; therefore metastases are most often localized in the interior walls of the abdominal cavity, especially the subphrenic space on the right as well as the greater omentum. Also, tumor dissemination occurs via the lymphogenic route, with tumor spreading to paraaortal and paracaval lymph nodes, those of the uterine broad ligament and pelvis, including the external iliac, obturator and epigastric groups. More seldomly, the tumor may spread to lymph nodes along the round ligament of the uterus, affecting the inguinal lymph nodes. In a late stage of the disease, sometimes secondary lesion of retroperitoneal lymph nodes is observed. Hematogenic metastases of ovarian cancer are observed very seldomly, mainly in the liver and lungs.

In the so-called preclinical stage of cancer development, any symptoms whatsoever are absent. Enlargement of the abdomen in consequence of ascites, pain syndrome, uterine hemorrhage, intestinal and dysuric disorders indicate tumor dissemination. In the preclinical stage, ovarian cancer is often detected accidentally during prophylactic gynecologic examination.

12.1 Methods of Diagnosis

Examining a patient suspected of ovarian cancer begins with internal gynecologic examination, with simultaneous mirror examination of the vagina and uterine cervix. The determination of the tumor marker CA-125 in blood has diagnostic significance, since its content in blood significantly increases in presence of ovarian cancer. US is the widest-spread and most available method of radiologic visualization for ovarian cancer. Use of transabdominal US has significantly increased the efficiency of diagnosis of ovarian masses compared with manual gynecologic examination, and introduction of transvaginal, rectal and intravaginal sensors with high resolving capacity extends the prospects of ultrasonography. The accuracy of US diagnosis is 85–94%. Further, some of its advantages are: rapidity and simplicity of examination, safety for the patients and for the diagnostician, painlessness, and the possibility of repeated dynamic observation. CT and MRI are also applied in this field. They permit assessment of the size of the mass, its relation with adjacent organs and tumor dissemination. The diagnostic value of these visualization methods is roughly the same as that in endometrial and cervical tumors. Unlike CT, the high sensitivity of MRI shows itself in imaging soft tissues.

The endoscopic methods of examination, in particular laparoscopy, are a firm part of the diagnostic arsenal as concerns detecting malignant ovarian tumors.

However, in performing these methods a number of unsolved questions arise, related to absence of specific changes in some forms of tumor growth, commissural process in the small pelvis and/or abdominal cavity as a consequence of previous surgical intervention or an inflammatory process. It is necessary to carry out a cytological examination of effusion and lavages from the abdominal and pleural cavities, as well as that of aspirate from the uterine cavity. This histological material may be used for assessing individual tumor sensitivity to cytostatic drugs.

12.2 PET Diagnosis

By now, some diagnostic experience of using ^{18}F -FDG PET in patients with ovarian cancer has been accumulated, but the results of numerous studies are ambiguous. According to Hubner et al. (1993), the positive prognostic value of the method in primary diagnosis and in assessing tumor dissemination was 86%, while its negative prognostic value was 76%. Schroder et al. (1999) determined a high level of the sensitivity and diagnostic accuracy of ^{18}F -FDG PET (96% and 90% respectively), whereas its negative prognostic value was 75%. The cystic type of adenocarcinoma is one of the sources of false-negative results in detecting the primary lesion and tumor dissemination. Metastasis of ovarian cancer is notable for multiple small-focal carcinomatoses of the peritoneum. Foci with size below 5 mm are not usually accessible to PET visualization. This significantly reduces the importance of the method in diagnosis of metastatic lesion of the peritoneum compared with laparoscopy (Rose et al. 2001). Nevertheless, according to other authors foci with size less than 5 mm are successfully diagnosed by means of ^{18}F -FDG PET (Smith et al. 1999; Drieskens et al. 2003; Turlakow et al. 2003).

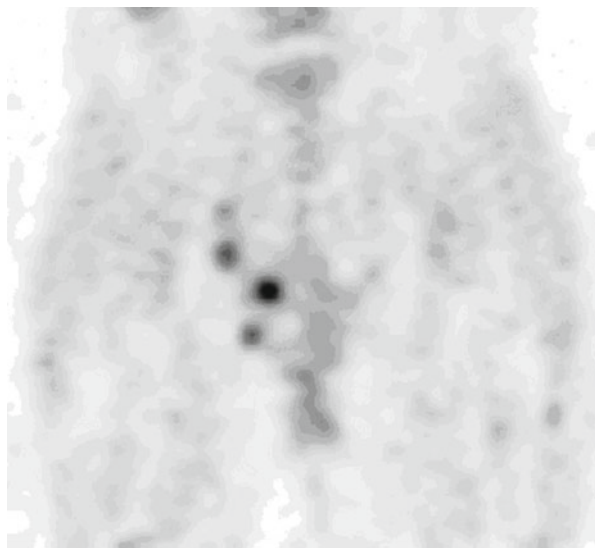
In their comparative analysis of the results of diagnostic laparoscopy and those of ^{18}F -FDG PET, Kim et al. (2004) showed a high prognostic accuracy of the latter in detecting secondary lesion of the peritoneum (93%).

Numerous studies have provided objective proof of the diagnostic superiority of ^{18}F -FDG PET over traditional methods of radiologic visualization in confirming recurrence of ovarian cancer, especially in persons with a high titre of the tumor marker CA-125 (Fig. 12.1). The sensitivity of PET in the diagnosis of a relapse was 83–91%, while that of CT and MRI ranged from 45% to 91%. A similar tendency has been observed concerning specificity: 66–93% for ^{18}F -FDG PET and 46–84% for traditional methods of radiologic diagnosis (Delbeke and Martin 2001; Takekuma et al. 2005; Nanni et al. 2005).

As for evaluating the efficiency of ovarian cancer treatment, PET has not received wide use (Schroder et al. (1999)).

Thus, ^{18}F -FDG PET provides reliable information for diagnosis of the primary lesion and metastatic dissemination, as well as for detecting and localizing an ovarian cancer relapse.

Fig. 12.1 ^{18}F -FDG PET in a patient with biochemical signs of recurrent cancer of the right ovary. Multiple metastatic lesions of the iliac lymph nodes



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Currently, cervical cancer is one of the widest-spread forms of malignant neoplasms. This disease occupies seventh place in incidence among all malignant neoplasms and third place in women (after mammary and colorectal cancers). Recently, a considerable increase in frequency of diagnosing different forms of cervical cancer in young women (up to 40 years old) has been observed.

Possible etiologic factors for developing cervical cancer include the early start of sex life, viral (human papilloma virus, HIV and genital herpes virus) and Chlamydia infections, a large number of sexual partners, traumas of the uterine cervix at child-birth and hereditary predisposition.

The main factors determining prognosis in patients with cervical cancer comprise the morphological texture of the tumor and the character and degree of tumor dissemination. It is accepted to distinguish two histological types of cancer of the uterine cervix: planocellular cancer accounts for 95–97% of all malignant neoplasms here, while 4.5% are adenocarcinomas. Undifferentiated cancer, melanoma, lymphoma and sarcoma are observed very seldomly (less than 1% of cases). It has been established that invasive planocellular cancer of the uterine cervix develops from the normal epithelium, passing through all the stages of precancerous dysplasia. Cancer in situ or preinvasive cancer is characterized by minimum signs of atypia and by absence of tumor dissemination beyond the basal membrane of the epithelium of the uterine cervix.

Cancer of the uterine cervix disseminates in three directions: to the vagina, to the uterine body and to the parametrium. In late stages the tumor may infiltrate the pouch of Douglas and urinary bladder. Lymphogenic metastasis occurs through lymph collectors of the parametrium to pelvic, iliac and, in still later stages, to paragastric lymph nodes. Hematogenic metastases of cervical cancer are most often observed in the lungs, liver and bones. In case of exophytic forms, as well as in the presence of mixed and endophytic tumor growth, a high frequency of lymphogenic metastasis is observed, while the vaginal variant of spreading is characterized by a lower metastasis rate. Adenocarcinoma is characterized by early metastasis and relapse (up to 12 months), while for planocellular cancer generalization is possible over 36 months.

The classification of cancer of the uterine cervix is presented in Table 13.1.

Table 13.1 TNM and FIGO classifications for cervical cancer

TNM	FIGO	Surgical-pathologic findings
Categories	Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
T1a	IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
T4	IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
T4a	IVA	Tumor invades mucosa of bladder or rectum (bullous edema is not sufficient to classify a tumor as T4)
T4b	IVB	Tumor extends beyond true pelvis
<i>Regional lymph nodes (N)</i>		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
<i>Distant metastasis (M)</i>		
M0		No distant metastasis
M1		Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal, or para-aortic lymph nodes; and lung, liver, or bone)

Cancer of the uterine cervix for long time has no clinical manifestations. Sometimes patients complain of abundant bloody or serous discharge from the vagina and hemorrhages. In case of small size of tumor there may be contact hemorrhages, which occur immediately after coitus. Later, pain syndrome appears. Pains are localized in the lumbar area, above the pubes and in the crotch. Pain syndrome usually intensifies when the tumor infiltrates the adjacent organs: the urethra, intestine, and urinary bladder.

13.1 Methods of Diagnosis

Diagnosis of cancer of the uterine cervix is rather simple and is based on the data of gynecologic examination, colposcopy, cytological and histological studies. Schiller's test with Lugol's iodine solution, which is done during colposcopy, permits the detection of Lugol-negative areas, suspected of cervical cancer. The pathophysiological basis of the test is a sharp decrease in glycogen content in pathologically changed layers of the integumentary epithelium of the uterine cervix. Oncocytological study consists of examining smears from the vaginal portion of the uterine cervix and cervical canal. Diagnosing is based on dividing smears into five classes according to the Papanicolaou classification:

Class 1 – absence of atypical cells

Class 2 – cells with signs of atypia in small amount

Class 3 – cells with marked signs of atypia

Class 4 – suspicion of malignant process

Class 5 – convincing signs of malignancy

Due to the possibility of false-positive results of oncocytological examination, final diagnosis is made on the basis of data of the histological analysis of biopsy material obtained under colposcopy control.

The radiologic diagnosis of cervical tumors is based mainly on the data of ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). US enables the detection of tumor localization, its size, form, structure and relation to other organs of the small pelvis. Use of intravaginal and intrauterine sensors significantly increases the information value of the method. CT is a poorly informative method of diagnosing in the early stages of the disease. However, in the late stages CT permits diagnosis of the primary tumor, determination of its spread to adjacent organs and the detection remote metastases.

MRI is an informative method of diagnosing cancer of the uterine cervix; it permits not only the detection of the malignant tumor but also the visualization of regional and remote metastases.

However, the main shortcomings of the indicated radiologic methods are based on the difficulty in differentially diagnosing the detected solid masses as well as in assessing the real size of the formation, particularly during treatment.

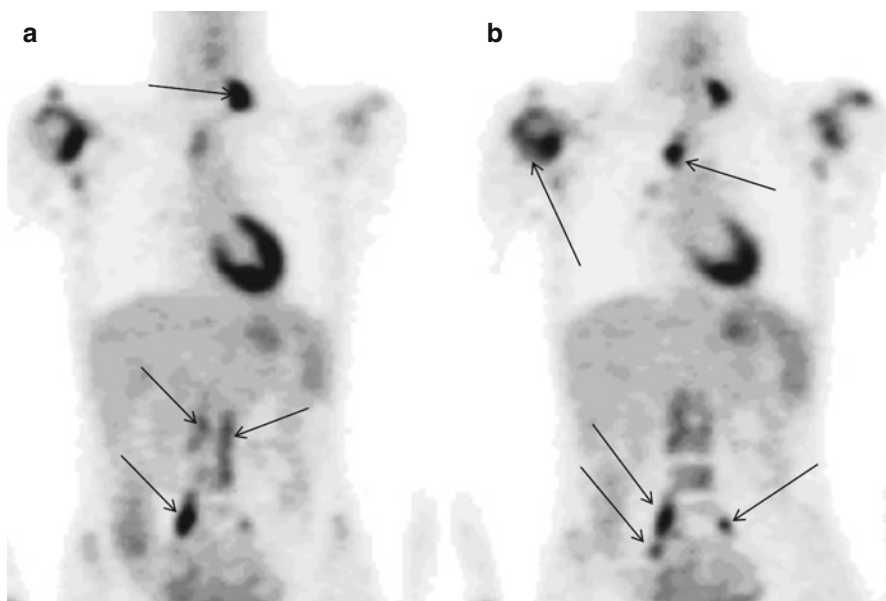


Fig. 13.1 ¹⁸F-FDG PET of a patient with disseminated cervical cancer. Multiple metastatic lesion of iliac, para-aortic, mediastinal and supraclavicular (*left*) lymph nodes and right humeral epiphysis (*arrows*). Inflammatory FDG uptake of different intensity in activated arthrosis of gleno-humeral joint

13.2 PET Diagnosis

Given that colposcopy is highly informative in diagnosing the primary lesion in cervical cancer, recourse to the expensive radiologic techniques is not always justified. This accounts for sparse information in the medical literature concerning the diagnostic accuracy of PET in detecting the primary tumor focus. In a study of Grit et al. (2001), high ¹⁸F-FDG accumulation in the primary tumor was demonstrated, with indices of metabolic activity in various histological types of cancer not differing significantly: in planocellular cancer the standardized uptake value (SUV) was 7.9 ± 5.7 , while in adenocarcinoma it was 8.2 ± 5.7 (Grit et al. 2001). Yen et al. (2002), in their turn, observed a close interrelation between the intensity of ¹⁸F-FDG uptake by the primary tumor, the degree of differentiation of cervical cancer and the expression of the GLUT1 receptors in tumor cells. The level of ¹⁸F-FDG accumulation in the primary focus is considered to determine the prognosis of the disease. For example, in a study by Jang et al. (2002) the life span of patients with planocellular cervical cancer was reported to be considerably lower in presence of high metabolic activity of the primary tumor focus.

Numerous studies report an extremely high diagnostic efficiency of ¹⁸F-FDG PET in assessing the dissemination of cervical cancer compared with traditional radiologic techniques (Fig. 13.1). The sensitivity of PET, according to research data of many centers, varies from 83% to 100%, and its specificity ranges from 89% to 100%. Meanwhile, the sensitivity of CT and MRI according to the same authors is

only 50–73%. In the study of Wong et al. (2004) the diagnostic accuracy of PET in assessing tumor dissemination is established as approaching 100%. In restaging cervical cancer, the sensitivity was 82% and the specificity 97%. When comparing MRI results with PET data, Park et al. (2005) observed the superiority of PET in detecting metastatic lesions of pelvic lymph nodes.

The meta-analysis of the results of 15 studies devoted to the diagnostic accuracy of ^{18}F -FDG PET in staging of cervical cancer has defined the sensitivity as 84% and specificity as 95% as regards metastases to retroperitoneal lymph nodes and 79% and 99% respectively in case of a secondary lesion of pelvic lymph nodes (Havrilesky et al. 2005).

The method of delayed scanning 3–4 h after the injection of ^{18}F -FDG permits improved accuracy of PET in diagnosing the primary lesion, a local relapse and metastatic lesion of pelvic, iliac and retroperitoneal lymph nodes (Lai et al. 2004; Ma et al. 2003). In the study by Yen et al. (2003), the results of delayed ^{18}F -FDG PET facilitated a change of therapeutic management in 30% of patients (Yen et al. 2003).

As is known, oncological disease prognosis is determined first of all by the stage of the disease and by tumor sensitivity to radiological therapy or chemotherapy. Given the high diagnostic value of ^{18}F -FDG PET in staging and in evaluating treatment efficiency, this method has much prognostic importance. The 3-year survivability of patients with cervical cancer of the IIIB stage (according to the FIGO classification (Benedet et al. 2000)) was 73% in absence of lymphogenic and hematogenic tumor disseminations. Tumor infiltration of pelvic lymph nodes was conducive to reduction of life span (3-year survivability decreased to 58%). Metastatic lesion of paraaortal lymph nodes reduced 3-year survivability down to 29% (Singh et al. 2003). Grisby et al. (2004) reported high 5-year survivability in cervical cancer patients with complete metabolic response to radiological therapy and chemotherapy according to ^{18}F -FDG PET data. In order to choose the right therapeutic management, Yen et al. (2004) suggested using ^{18}F -FDG PET in combination with a risk stratification system developed by them and based on three prognostically unfavorable factors: radiological therapy in the anamnesis, SCC antigen titre above 4 ng/mL and presence of clinical signs of the disease. The authors think that ^{18}F -FDG PET should be performed on patients with risk indices of 1 and 2, since it is in this category of persons that a radical treatment regimen can be carried out (Chang et al. 2004).

Hypoxia is known to be a prognostically unfavorable factor diminishing tumor sensitivity to radiological therapy. The introduction into clinical practice of a new radiopharmaceutical (RP) for assessing tumor oxygenation (^{18}F -misonidasol and ^{62}Cu -diacetytle-bi-N4-metylethiosemicarbason) will permit the diagnostic capacities of PET to be extended. In their study, Dehdashti et al. (2003) reported successful ^{62}Cu -diacetytle-bi-N4-metylethiosemicarbason PET results in the prognosis of the life span of patients with cervical cancer.

^{11}C -Labeled RPs (^{11}C -choline, ^{11}C -methionine and ^{11}C -acetate) have not received wide use in oncologic gynecology due to their low tumor specificity. The few publications on this account indicate comparable sensitivity values of ^{18}F -FDG PET and PET with ^{11}C -labeled RP (Torizuka et al. 2003; Lapela et al. 1994).

13.3 Endometrial Cancer (Cancer of the Uterine Body)

During the last decade a steadfast growth of endometrial cancer incidence has been observed. In developed countries such as Sweden and USA endometrial cancer has taken the first place in frequency. In Russia more than 14,000 women develop endometrial cancer annually. Endometrial cancer is more often observed in women over 50 years old. One of the triggers of carcinogenesis in endometrial cancer is considered to be associated with hormonal disbalance. Women suffering from metabolic syndrome (arterial hypertension, obesity, pancreatic diabetes) are predisposed to this disease.

Among precancerous states there are chronic endocervicitis, endocervicosis, adenomatosis, endometrial polyps, leukoplakia, cicatricial changes after childbirth and abortions.

The transformation from precancer to cancer usually takes from 2 to 15 years. As concerns the histological texture, endometrial cancer is usually represented by adenocarcinoma. Mucous, epidermoid and undifferentiated cancers are observed more seldomly.

The classification of endometrial cancer by stages is based on the degree of its dissemination. In the first stage, the tumor is localized within the endometrium; stage IIa is characterized by infiltration of the myometrium, while stage IIb is characterized by unilateral or bilateral infiltration of the parametrium, not reaching the walls of the small pelvis; in stage IIb, cancer spreads to the uterine cervix. In the third stage, infiltration of the parametrium spreading to the wall of the small pelvis is observed. In stage IIIa, metastases to regional lymph nodes, to the uterine appendages and vagina are observed; in stage IIIb, peritoneal carcinomatosis is observed. Tumor invasion of the adjacent organs (the urinary bladder, rectum and others) as well as presence of remote metastases indicate stage IV of endometrial cancer.

The probability of emergence of lymphogenic metastases is largely determined by the depth of tumor invasion. If the malignant neoplasm is localized within the mucous membrane or in case of superficial invasion of the myometrium below 5 mm, metastases are detected in 2.5% of patients. If the depth of invasion increases more than by 1 cm, the frequency of metastatic lesion increases up to 46.1%.

Tumor recurrence and metastasis in 75% of patients emerge within 3 years after primary treatment. Dissemination occurs mainly through lymphatic viae. Metastasis occurs to pelvic lymph nodes situated along iliac and hypogastric vessels or obturator nerve, more seldomly through the lymphatic viae of the round ligament of uterus to inguinal lymph nodes.

Cancer spreads from the endometrium to the myometrium, uterine tubes and ovary. Remote metastases are observed in the liver, lungs, bones and brain.

The clinical course in endometrial cancer is relatively favorable. The general well-being of patients long remains satisfactory. The main symptom of the disease is bloody discharge from the vagina. Abundant hemorrhages occur in case of considerable size of the tumor or in its necrosis. Pain syndrome appears only in late stages. Intense pains occur in case of compression of nerve plexus by tumor

infiltrate of parametral tissue or by affected lymph nodes. Tumor spread to adjacent organs (the urinary bladder, rectum, etc.) manifests itself with corresponding symptoms.

13.4 Methods of Diagnosing

The diagnosis of endometrial cancer is usually made by way of morphological study of material from the uterine cavity obtained by aspiration or by separate diagnostic curettage. The role of the traditional methods of examination, which were long used in gynecology (hysterosalpingography, pneumopelvigography, angiography, lymphography), is now limited, so the main methods of radiologic visualization are US, CT and MRI. US examination with use of intravaginal and intrauterine sensors is an efficient method of diagnosing uterine tumors. The sensitivity of US reaches 70–80%. However, sonography permits the visualization of tumors with diameters above 1 cm. Some authors point out the possibility of using US for planning intracavitary therapy and assessing the efficiency of therapy. CT is also widely used in diagnosing endometrial cancer and permits assessment of the dissemination of tumor process. However, CT is not efficient in the early stages of the disease.

MRI is considered to be a more efficient method in diagnosing uterine cancer, since it provides a good visualization of the endometrium. It permits detection of the primary tumor focus in the early stages of the disease. Obtaining images in three projections as well as high tissue specificity permits distinct visualization of the contours of the primary tumor and its relations to the surrounding organs and vessels as well as the state of lymph nodes. However, the sensitivity of the method is not high compared with its specificity and diagnostic accuracy (68.5%, 92.8% and 89.2%, respectively).

In order to specify the areas of regional metastasis, contrast roentgenolymphography is used. Its diagnostic accuracy reaches 85%. However, the invasive character of the procedure, elderly age of patients, presence of severe concomitant diseases and endocrine disorders are often an obstacle to performing direct lymphography.

In spite of the wide range of available diagnostic means, the differential diagnosis and determination of the stage of the disease still remain a pressing problem and require further improvement of visualization methods.

13.5 PET Diagnosis

The accumulated experience of PET diagnosis of endometrial cancer confirms high efficiency of this method in disease staging, early detection of relapses and treatment efficiency evaluation. Belhocine et al. (2002) established that ^{18}F -FDG PET shows 96% sensitivity in diagnosing endometrial cancer recurrence, including patients without clinical-instrumental signs of the disease. The study of Saga et al. (2003) indicated the diagnostic advantage of ^{18}F -FDG PET (93% accuracy) over

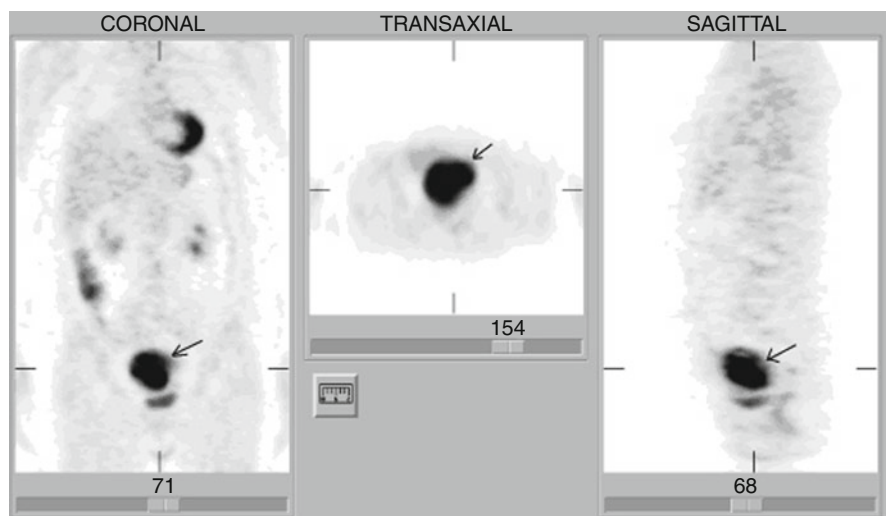


Fig. 13.2 Pathological ^{18}F -FDG uptake (*arrow*) in a patient with uterine myosarcoma (slices are done along the transaxial, sagittal and frontal projection)

traditional methods of radiologic visualization (85% accuracy) and biochemical indices of endometrial cancer recurrence (83% accuracy). The authors drew the conclusion that in one-third of patients the treatment regimen is changed on the basis of PET data and in case of negative PET results there is an increase in the length of relapse-free period.

Sarcoma should be also mentioned in this chapter on malignant endometrial neoplasms. Uterine sarcoma is a rare disease and it makes up only 5% of all malignant neoplasms of this localization. Consequently, the medical literature data on PET diagnosis of uterine sarcoma are sparse.

Umesaki et al. (2001) observed a high level of ^{18}F -FDG accumulation in tumor nodules. Afterwards the same authors concluded that ^{18}F -FDG PET has high accuracy, comparable with that of MRI (Umesaki et al. 2001). In the clinical practice of the RSCRSST there has been only one patient with endometrial myosarcoma (Fig. 13.2).

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Prostate cancer is one of the most frequent neoplasms in middle-aged and elderly men. In a number of countries this tumor is the second or third most frequent in incidence among all oncological diseases. Mortality from prostate cancer occupies the second place after lung cancer among all oncological diseases.

Presently some risk factors for this disease are known, such as age, race, genetic factors, nutrition characteristics, hypodynamia, etc. The probability of developing prostate cancer increases after the age of 50 and more than 70% of cases of prostate cancer are detected in males over 65. Up to 40% of males at the age of 60–70 have microscopic cancer of the prostate. Due to some characteristics of clinical course the disease may not have any impact on the patient's well-being for many years. Only in 10% of cases the latent form of prostate cancer passes to its symptomatic form. It has been established that the risk of developing the disease grows when an excessive amount of animal fats is consumed. Some substances, for example vitamins of the B group, vitamins D and E and the mineral selenium, decrease the risk of developing prostate cancer. Hereditary predisposition to the disease should be taken into account.

Histological studies on prostate cancer have permitted to establish specific injuries preceding the occurrence of the disease. The direct predecessor of invasive adenocarcinoma is prostatic intraepithelial neoplasia (PIN), which can be detected only by way of biopsy. Unlike prostate cancer, in the stage of PIN the basal cell membrane remains intact, surrounding tissues are not affected and the level of prostate-specific antigen (PSA) remains normal.

Prostate cancer is a hormone-dependent tumor, whose growth is conditioned by the influence of androgens, first of all dihydrotestosterone (DHT), a functionally active form of testosterone.

14.1 Pathologic Anatomy and Way of Metastases

Prostate tumors are morphologically divided into epithelial and nonepithelial tumors. The vast majority of prostate tumors (more than 99%) are epithelial; epithelial tumors, in their turn are in 98% of cases represented by adenocarcinoma.

Adenocarcinoma is microscopically inhomogeneous. There are acinic cell, small cell (scirrhous), clear cell, ductal and mucinous histological forms of adenocarcinoma of the prostate. Most histological classifications are based on signs of differentiation of prostate cancer. Three tumor gradations are distinguished: highly differentiated, moderately differentiated and lowly differentiated adenocarcinomas. Prostate cancer almost always has an inhomogeneous structure. This is the basis of Gleason's histological classification, which has received universal recognition. According to the Gleason scale, a grade 1 tumor is characterized by the presence of practically normal glands. As the Gleason scale increases, glandular structures become inhomogeneous, their size and configuration become irregular and tumor boundaries become indistinct. At grade 5, glands are practically absent and the tumor has a solid texture. The sum of grades according to the Gleason scale is composed of the dominant and the second in frequency types of glands; for example, $3 + 5 = 8$. The obtained number is an important prognostic criterion permitting conjecture on the degree of dissemination, presence of metastases and to make prognosis of the disease.

Prostate cancer spreads by ways of local invasion, lymphogenic and hematogenic metastases. Local invasion often precedes the emergence of metastases. Tumor most often spreads to the prostatic capsule and affects the base of the urinary bladder and seminal vesicles. Spread of prostate cancer to the urethra is possible. Denonvilliers' fascia serves as a barrier between the prostate and the rectum; therefore invasion to the rectum is far less frequent. Lymphogenic metastases most often affect obturator lymph nodes. The next frequent localization of metastases is in the internal iliac, presacral and external iliac lymph nodes. There are two ways of hematogenic spread of prostate cancer: arterial and venous. The hematogenic arterial way characterizes prostate cancer metastases to the lungs, liver, brain and bones. The exception is only the bones of the pelvic girdle, whose specific lesion occurs in the venous way. Metastases most often affect the bones. Bone metastases are observed in 80% of patients who die from prostate cancer. In most cases they have an osteoblastic character, even though lytic and mixed lesions are observed as well. The most frequent localizations of bone lesions are the spine, femoral bones and pelvic bones.

In the initial stages prostate cancer does not manifest itself clinically. It is usually detected accidentally during morphological study of material obtained by transurethral resection or prostate biopsy in patients with elevated PSA indices.

The development of symptoms is associated with enlargement of the organ and emergence of regional and distant metastases. The increase in volume of the prostate leads to the development of symptoms of obstruction of the urinary bladder: frequent and difficult urination, feeble stream, etc. The intensity of obstruction symptoms is directly associated with the degree of tumor compression of the urethra. Symptoms of obstruction of the urinary tracts are usually accompanied by a number of other disease manifestations. For example, if the tumor invades into the prostatic urethra, hematuria and painful urination occur. If the sphincter muscle of the urethra is tumor-affected, urinary incontinence develops. Locally spread prostate cancer may compress and spread to the distal section of the rectum. In such cases the disease manifests itself with constipations, tenesmus, hemorrhages, and excretion of mucus from the rectum.

In some patients, clinical manifestations of the disease are determined by metastases to lymph nodes. However, the main motif that brings the patient to take medical advice is pain syndrome caused by bone metastases. Localization of pain sensations usually corresponds to the location of metastases. Metastases to the spine may lead to paralyses and pareses.

14.2 Methods of Diagnosis

The standard diagnosis of prostate cancer is based on the results of digital rectal examination, level of PSA in blood serum and transrectal US. On the basis of these data, transrectal multifocal biopsy of the prostate with ultrasound aiming is administered.

Digital examination of the rectum is the simplest, cheapest and safest method of diagnosing prostate cancer. The characteristic features of this disease are enlargement, changed consistence, presence of dense nodes, asymmetry and disturbance of mobility.

One of the main methods of early detection of prostate cancer is PSA blood test, which should be done annually in all males over 50. If prostate cancer has been detected in relatives, such tests should be implemented starting from 40 years. However, in a quarter of cases prostate cancer can be detected also in case of normal PSA levels in blood serum. This is accounted by particular characteristics of the tumor. Also, increase in PSA level in blood is not always associated with a malignant prostate neoplasm. This index may rise in such diseases as benign hyperplasia of the prostate (adenoma), acute and chronic prostatitis as well as after digital rectal examination of the prostate, coitus, etc. It should be remembered that lowly differentiated prostate adenocarcinoma produces much less PSA than highly differentiated forms of cancer do, which makes interpretation of results of a single test difficult.

US of the prostate not only helps detect the tumor but also may be of aid in performing biopsy of a suspicious area. For screening diagnosis of prostate cancer, the transabdominal method of examining the prostate is widely used. However, the capacities of this method of diagnosis are limited. The indicated methodology permits determination of the size and symmetry of the gland, assessment of the state of the capsule, the volume of residual urine and detection of gross changes in the pelvic organs. At the same time, the detection of subtle changes in the internal structure of the prostate and assessment of the character of pathologic changes are possible only by means of transrectal US examination. The simplicity of performing transrectal US and its high information have significantly extended the possibility of early diagnosis of prostate diseases. A valuable advantage of transrectal US is its ability to provide data on the size of the prostate and on its topographic-anatomic relation with adjacent organs and tissues, the state of its capsule and internal structure. And yet US examination has serious limitations in determining the stage of the tumor process. The information value of transrectal US is confined to a small field. The sensitivity and specificity of a standard transrectal US examination, according to different authors, range from 38% to 58% and from 42% to 60%, respectively (Kattan et al. 1998; Rifkin et al. 1990; Smith et al. 1997).

Table 14.1 Comparison of conventional methods of diagnosis of prostate cancer local recurrence (Schoder and Larson 2004)

Method	Sensitivity (%)	Specificity (%)
DRE	44	91
TRUS	75	67
CT	36	–
MRI	95	100

A new method that has appeared recently, that of US angiography, provides the unique possibility to quickly obtain in a noninvasive way reliable diagnostic information on vessels, and to study the hemodynamics and perfusion of the prostate, which improves the possibilities of diagnosing prostate cancer.

CT is considered to be lowly informative in case of small size of the tumor focus (less than 2 cm) located within the organ, because of small difference in density between tumor tissue and normal tissue. The diagnostic accuracy of CT in detecting a tumor spreading beyond the prostate gland is 24%, while if seminal vesicles are tumor-affected, it is 69% (Hricak et al. 1987). However, in late stages of the disease, spiral CT permits assessment of the dissemination of the pathologic process, in particular presence or absence of tumor tissue infiltration of the urinary bladder and rectum, as well as those of regional and distant metastases.

MRI of the prostate has a number of advantages over CT and transrectal echography. In particular, this method of visualization, due to the possibility of obtaining images in three planes, reflects with high accuracy the size of the prostate, its contours, the topographic-anatomic relations of the prostate with periprostatic organs and tissues. The information value of the examination significantly increases when a rectal coil is used. Endorectal MRI may be a valuable supplement to transrectal US. Images obtained in endorectal examination are characterized by a more distinct differentiation of the zonal structure and capsule, which is particularly important in cases when routine MRI does not permit to precisely determine the boundaries of the tumor node. MRI can diagnose with high accuracy tumor spreading into the perineural tissue, which is of importance for choosing the volume of surgical intervention. The sensitivity of the method is 50%, its specificity being 95%. The accuracy of endorectal MRI makes up approximately 80% (Yu and Hricak 2000). The sensitivity of MRI in detecting lymphogenic prostate cancer metastases, according to some authors, is 51–89%, using special lymphotropic contrast agents the sensitivity increases up to 90% (Bartolozzi et al. 1996; Tempany et al. 1994; Harisinghani et al. 2003). False-negative MRI results in diagnosing lymphogenic metastases of prostate cancer are usually due to unchanged sizes of affected lymph nodes.

Table 14.1 summarizes the efficacy of traditional methods in diagnosing a local relapse of prostate cancer. The most effective in diagnosing local relapses of prostate cancer is MRI and, consequently, preference should be given to this radiological technique.

Radionuclide methods of examination for diagnosing primary tumor lesion in prostate cancer cases have not become widespread. However, there is a radiopharmaceutical (RP), ProstaScint, which is a ^{111}In -labeled mouse monoclonal antibody, 7E11-C5.3, that is directed toward a glycoprotein expressed by prostate epithelium known as prostatic-specific membrane antigen (PSMA).

By means of scintigraphy it is possible to detect not only the primary lesion but also metastatic lesion of regional lymph nodes as well as distant bone metastases. Due to high specificity of examination with monoclonal antibodies, the information value of this method in diagnosing metastatic lesions of the bone tissue is much higher than that of ^{99m}Tc -pyrophosphate scintigraphy. Unfortunately, ProstaScint has not become widespread in Russia due to the expensiveness of the RP.

Until recently ^{99m}Tc -pyrophosphate scintigraphy of the skeleton was obligatory in the staging of prostate cancer. Scintigraphy of the skeleton is a highly sensitive method of diagnosing metastases to the bones, considerably superior to rentgenography, clinical examination and indices of alkaline phosphatase. False-positive results are observed in patients with bone fractures and degenerative dystrophic diseases of the locomotor system. The frequency of false-negative results does not exceed 1%. The probability of presence of bone metastases in the case of a PSA level lower than 10 ng/mL is virtually equal to zero. In most clinics, if the PSA blood content is less than 10 ng/mL, routine examination of the osseous system is no longer implemented. Nevertheless, implementing radionuclide scanning is obligatory in prostate cancer patients with PSA blood content levels higher than 10 ng/mL, pain in the bones or high readings of alkaline phosphatase.

14.3 PET Diagnosis

In Table 14.2, the comparative characteristics of RPs used in the diagnosis, staging and evaluation of prostate cancer treatment are listed.

It has been established that using ^{18}F -FDG PET for the early diagnosis of primary lesion in patients with prostate cancer is poorly efficient, since in most cases of prostate adenocarcinoma a low level of carbohydrate metabolism is observed, which

Table 14.2 Comparative characteristics of radiopharmaceuticals for the diagnosis of prostate cancer

Characteristic	^{18}F - FDG	^{11}C - methionine	^{11}C - choline	^{18}F - choline	^{11}C - acetate	^{18}F - fluorodihydro- testosterone
Excretion way	Urinary tract	Urinary tract	Bowel	Urinary tract	Bowel	Bowel
Excretion by urinary system	+++	++	—	++	—	—
Diagnosis of the primary tumor	No	No	Yes	Yes	Yes	No
Diagnosis of regional metastases	No	No	Yes	Yes	Yes	No
Diagnosis of recurrence	+	?	+++	++	+++	No
Identification of distant metastases	+	++	+++	+++	+++	No
Predictive value	+	?	?	?	?	?
Evaluation of the treatment effectiveness	++	?	?	?	?	+

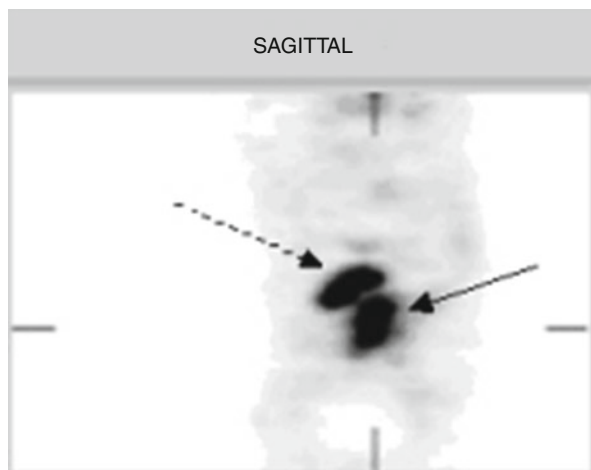


Fig. 14.1 ^{18}F -FDG PET in sagittal projection of a patient with prostate cancer, T4N2M1. In projection of prostate lobe a focus of pathological ^{18}F -FDG uptake is found (arrow). Physiological uptake in the urinary bladder (dotted line arrow)

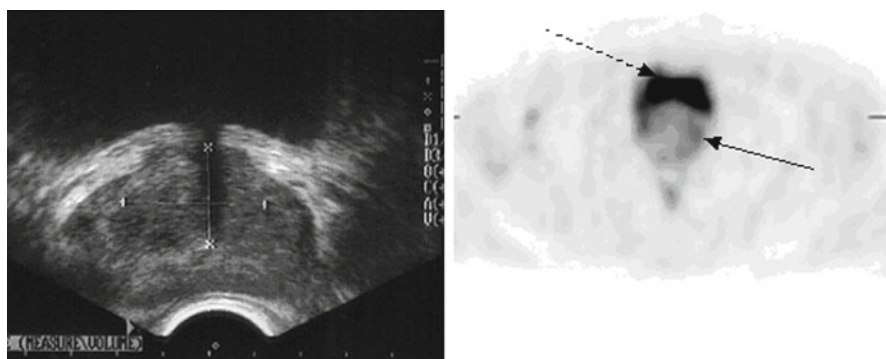


Fig. 14.2 Transrectal USD and ^{18}F -FDG PET results – axial projection in a patient with histologically proved prostate cancer, T₃N₀M₀. There is unspecific isometabolic FDG uptake in the enlarged prostate. Both methods show impression of the urinary bladder by the enlarged prostate. In projection of the USD-detected solid mass in the prostate a focus is observed, which deforms the posterior wall of the urinary bladder (arrow). Physiological uptake in the urinary bladder (dotted-line arrow)

entails low ^{18}F -FDG uptake by neoplasm cells in the prostate. In Figs. 14.1 and 14.2, different variants of ^{18}F -FDG uptake in primary tumor foci in patients with prostate cancer are presented. ^{18}F -FDG PET sensitivity is only 65% (Hoh et al. 1996; Shreve et al. 1996). Experimental studies on a fast-growing prostate cancer cell clone with phenotype DU145 permitted the observation of high glucose consumption by tumor cells. In a slow-growing cell clone of prostate cancer with phenotype LNCap, the amount of glucose consumed by cells was not big (Singh et al. 1999).

Another problem of visualizing prostate neoplasms is associated with ^{18}F -FDG excretion by the kidneys and consequently with high RP uptake in the urinary bladder. This is why some researchers suggest catheterizing the urinary bladder during examination and taking diuretic medicines for the purpose of rapid RP excretion, in order to improve visualization of the primary lesion (Liu et al. 2001; Effert et al. 1996). This procedure makes the examination more difficult but it does not remove the main problem – low ^{18}F -FDG uptake in prostate tumors.

A higher sensitivity in diagnosing primary tumor lesions and local relapses has been established for ^{11}C -acetate. ^{11}C -Acetate uptake by tumor cells reflects the lipid synthesis rate. This has been proved on the basis of experimental studies (Schoder and Larson 2004). In normal cells of the prostate, citrate synthesis and uptake in mitochondria are increased. On the other hand, in tumor cells of the prostate, the citrate concentration decreases sharply. Besides, some portion of the citrate comes out of mitochondria into cell cytoplasm and turns into oxaloacetate and acetylcoenzyme A, which are the sources of cell membrane lipid synthesis. A high concentration in prostate cancer cells of the enzyme lipid synthetase (FAS), responsible for lipid synthesis, should be noted. Direct correlation has been observed between tumor growth rate and the concentration of lipidsynthetase. Additionally, ^{11}C -acetate is included in intracellular phosphatidylcholine.

In clinical studies, a higher sensitivity of ^{11}C -acetate PET compared with ^{18}F -FDG PET has been demonstrated in diagnosing the primary cancer, local relapses and prostate cancer metastases. The sensitivity of the method in diagnosing a local relapse according to different studies was 59–83%, while that of metastases to lymph nodes was 75% (Schoder and Larson 2004). Additionally, ^{11}C -acetate excretion occurs through the respiratory system, which facilitates visualizing malignant neoplasms of the organs of the small pelvis.

It should be noted that ^{11}C -acetate is not a tumor-specific RP; therefore its high uptake is observed in unchanged prostate tissue or in benign prostate hyperplasia, which is the source of false-positive results.

Choline is one of the components of phospholipids included in the structure of the cell membrane. In addition, choline takes part in transmembrane transport and in lipid and cholesterol metabolisms and participates in transmembrane signal transmission. When choline gets into a cell, it enters into biochemical reactions, from which phosphoryl choline (under the effect of choline kinase), acetylcholine or betaine result. According to experimental data, both the amount and activity of choline kinase increase in prostate cancer cells and, correspondingly, choline uptake and phosphoryl choline concentration increase. These biochemical characteristics are at the basis of visualizing the primary cancer and metastases with use of choline labeled with ^{11}C or ^{18}F . An interrelation between the level of uptake of labeled choline in the prostate and the degree of tumor malignancy according to the Gleason scale has not been observed.

Currently two RPs have been developed on the basis of choline: ^{11}C -choline and ^{18}F -choline. The advantage of ^{18}F -choline is a longer half-life period, which makes it possible the use of this RP in medical institutions not equipped with a cyclotron. Among the shortcomings of this RP, its excretion through the urinary tract should be mentioned, which leads to poor visualization of the organs of the small pelvis.

Labeled choline is not a tumor-specific RP. Uptake of labeled choline in the prostate in benign hyperplasia is higher than in the normal prostate but lower than that in the tumor. Some authors indicate nonspecific ^{18}F -choline uptake by granulocytes and macrophages and ^{11}C -choline uptake in lymph nodes in reactive inflammation.

^{11}C -Methionine uptake reflects elevated transmembrane amino acid transport and, in part, protein synthesis, which is a marker of proliferative cell activity. The level of ^{11}C -methionine uptake in a tumor nodule is directly proportional to the number of viable cells.

On the basis of clinical data, the information values of ^{11}C -methionine PET and ^{18}F -FDG PET are roughly the same for androgen-non-sensitive prostate cancer (the primary focus and metastases). ^{11}C -Methionine is not excreted from the organism with urine, which facilitates visualizing the primary cancer and regional lymph nodes.

Androgen receptor expression takes an important part in the process of prostate cancer cell growth and proliferation. In fact, all the patients with prostate cancer initially respond to treatment aimed at androgen level reduction, but finally the tumor resumes growing in spite of low androgen level. The tumor becomes androgen-independent and is characterized by a more aggressive course.

Visualization of androgen receptors, assessing their quantity or their medicinal block, is a promising approach to evaluating the efficiency of antiandrogen antitumor therapy. ^{18}F -Fluorodihydrotestosterone is a labeled analog of dihydrotestosterone – the primary androgen receptor ligand. High ^{18}F -fluorodihydrotestosterone uptake in prostate tumor suggests its high sensitivity to androgens and speaks in favor of the efficiency of antiandrogen antitumor therapy. Low ^{18}F -fluorodihydrotestosterone uptake, combined with high ^{18}F -FDG uptake, indicates an androgen-independent type of prostate cancer, which is characterized by a more aggressive course and is prognostically unfavorable.

A number of authors observe high specificity of the method in diagnosing regional and distant prostate cancer metastases (Heicappell et al. 1999; Sanz 1999). For example, in the study of Hellicapell et al. (1999) a presurgical ^{18}F -FDG PET examination of the small pelvis was performed on patients, with subsequent histological assessment of the intraoperative material. A metastatic lesion of regional lymph nodes was detected by means of PET in most patients. False-negative results were conditioned by the small size of the metastatic focus (less than 5 mm). False-positive results were not observed in the study. In other works, the sensitivity of PET was no more than 50% and its specificity was up to 90% (Sanz et al. 1999). It should be noted that in all the studies ^{11}C -acetate PET was superior in sensitivity to ^{18}F -FDG PET (75% against 30%) (Schoder and Larson 2004). The sensitivity of ^{11}C -methionine in detecting metastases to lymph nodes was 70% (Fig. 14.3) (Schoder and Larson 2004).

Data on the capacities of ^{18}F -FDG PET in the diagnosis of distant prostate cancer metastases are ambiguous. The study of Seltzer et al. (1999) included 45 patients with elevated titre of PSA. All of them received treatment of the primary focus (surgical, radiological or cryotherapy). PET detected distant metastases in 50% of patients with PSA level above 4 ng/mL and only in 4% of patients with low PSA level (Fig. 14.4). On the whole, the study determined virtually the same accuracy for PET and CT in diagnosing distant metastases. In a later study, Nunes et al. (2002)

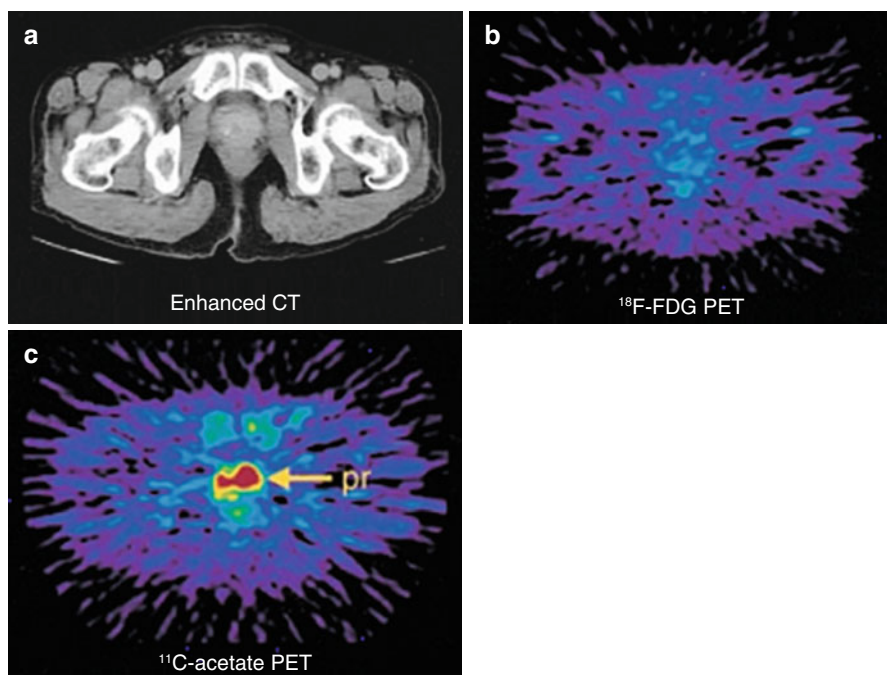


Fig. 14.3 CT (a), ^{18}F -FDG PET (b) and ^{11}C -acetate PET (c) of a patient with prostate cancer (by courtesy Nobuyuki Oyama et al., J Nucl. Med., 2002). Only ^{11}C -acetate PET shows positive uptake as sign of malignancy. In CT projection of the X-ray detected solid mass in the prostate pathologic uptake is detected only by ^{11}C -acetate PET

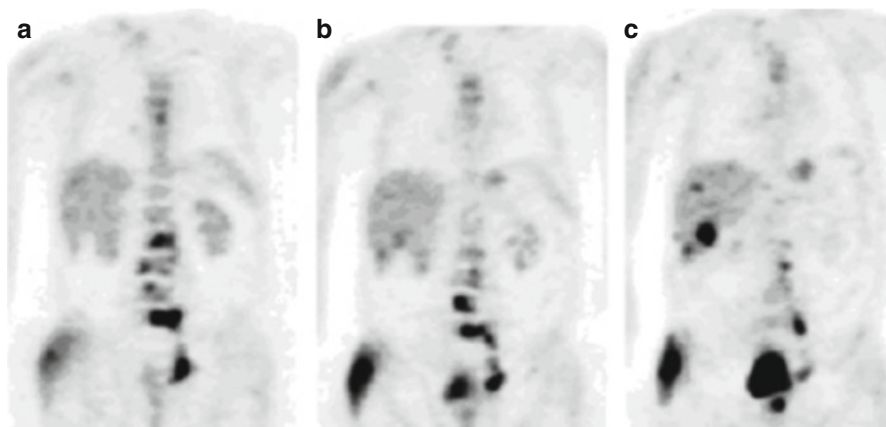


Fig. 14.4 ^{18}F -FDG PET in a patient with prostate cancer and multiple metastatic uptake in iliac and retroperitoneal lymph nodes, in the skeletal (vertebra, iliac bones) and in the liver

compared the traditional methods of radiological diagnosis with ^{18}F -FDG PET for diagnosing distant metastases in patients with increase in titre of PSA after treatment. The sensitivity of ^{18}F -FDG PET in detecting metastases to organs was 48%, while that of detecting bone metastases was 34%. Nevertheless, in another study the sensitivity of ^{18}F -FDG PET in detecting bone metastases proved to be higher than that of ^{11}C -acetate (86% against 57%) (Oyama et al. 2002).

At the same time, the studies of Schirrmeister et al. (1999) showed that PET detects bone metastases of small size twice as frequently as skeleton scintigraphy does. ^{18}F -FDG PET provides information on the biological activity of bone metastases and detects the presence of viable tumor cells. ^{99}Tc -Pyrphotech osteoscintigraphy, in its turn, reflects only the pathological activity of osteoblasts.

The method of PET/CT with Na^{18}F in diagnosing bone metastases is very attractive and till now most of the studies comparing Na^{18}F PET/CT with conventional scintigraphy or tumor specific tracers like ^{18}F fluorocholin or ^{11}C -acetate describe advantages of Na^{18}F over conventional bone scintigraphy and comparable results to Cholin or Acetate PET (de Arcocha et al. 2012).

Experimental and clinical studies have confirmed the considerable role of PET in the efficiency evaluation and monitoring of tumor therapy.

According to an experimental study, the level of ^{18}F -FDG uptake in cancer cells decreases to 62% of its initial values as soon as 48 h after androgen blockade and then goes down to 32% of its initial values 10 days after androgen blockade (Agus et al. 1998). The biochemical changes of a tumor cell always precede increase in size of a tumor and in PSA level. According to clinical studies, ^{18}F -FDG uptake decreases by 12% 1 month after androgen blockade and by 77% 5 months after it (Oyama et al. 2001). The reduction of ^{18}F -FDG uptake was directly proportional to the decrease in PSA level. An examination with ^{11}C -choline also has detected a considerable decrease in RP uptake after androgen blockade.

It should be noted that ^{18}F -FDG should be preferred in monitoring the therapy of bone metastases, since the results of osteoscintigraphy may be falsely positive in consequence of a rise in blood flow in the bones or increase in osteoblast activity and they may not reflect the progression of tumor process (Fig. 14.5). The results of ^{18}F -FDG PET demonstrate the quantity of viable tumor cells in bone metastases (Schoder and Larson 2004).

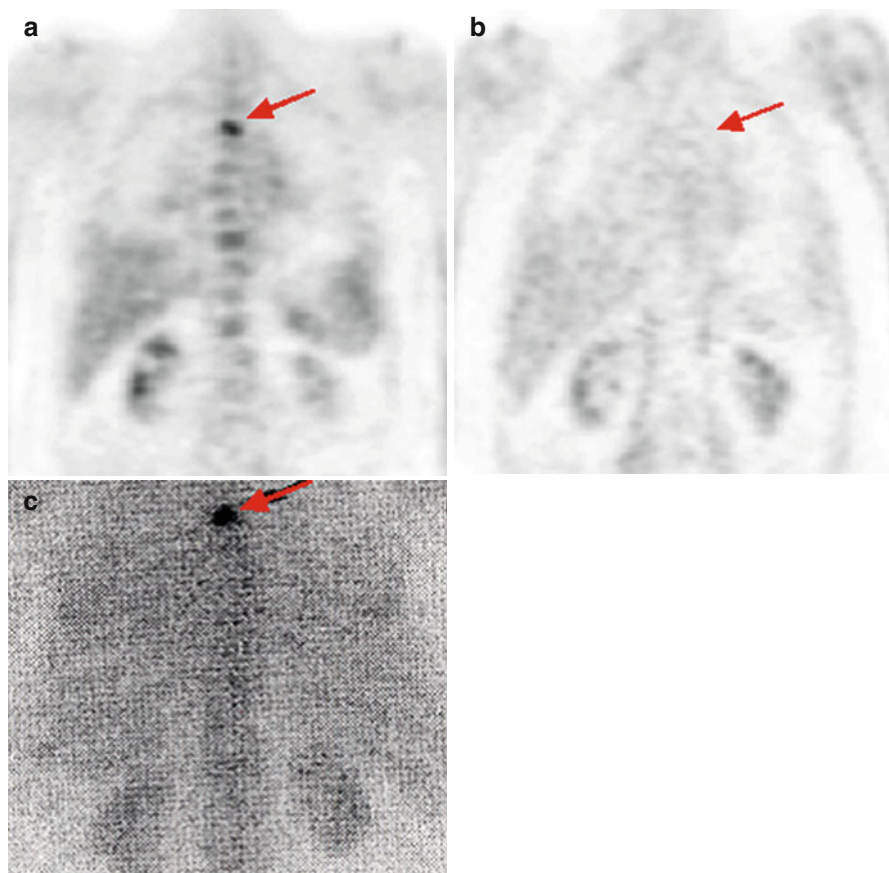


Fig. 14.5 ^{18}F -FDG PET (a) of a patient with prostate cancer and metastatic FDG uptake in the body of the 4th thoracic vertebra before the onset of hormone-radiological therapy. 2 months after the end of radiotherapy the restaging ^{18}F -FDG PET (b) showed no pathologic uptake. $^{99\text{m}}\text{Tc}$ -pyrphotech skeleton scintigraphy (c) showed increased activity in the 4th thoracic vertebra. Both findings confirm the metabolic inactivity and repair mechanism of the former metastatic lesion

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Cancer of the testicle is a rare disease which makes up about 1% of all malignant neoplasms in men. Malignant tumors of the testicle are most often observed at the age of 0–4, 30–34 years and over 75 years. In spite of a large number of studies devoted to the epidemiological characteristics and risk factors of testicular cancer, the etiology of this form of tumors is not completely clear (Buetow 1995). Among the main factors favoring the development of the disease there are cryptorchism, traumas of the testicle, genetic anomalies, in particular Klinefelter's syndrome, sterility and different kinds of electromagnetic radiation.

In 22–25% of cases testicular cancer develops in men with cryptorchism. During embryogenesis the testicles appear and develop in the abdominal cavity, but by the moment of birth they descend to the scrotum. However, in 3% of children one testicle or both of them either remain in the abdominal cavity or stop their descent in the inguinal area. Implementing a surgical intervention before adolescence in persons with cryptorchism decreases the risk of developing testicular cancer.

Besides that, family predisposition to cancer of the testicle is retraced. Several studies have confirmed that consanguinity of the first degree is a risk factor. The probability of developing testicular cancer is two- to four-times higher for the fathers and sons of patients than it is in the normal male population, and it is roughly eight- to ten-times higher for the brothers of such patients (Heimdal et al. 1996). In men infected with HIV, a high risk of testicular cancer is reported. This risk is particularly high in the presence of clinical symptoms of AIDS. Cancer in one testicle in the history increases the risk of tumor in the other.

In men suffering from infertility, usually hypotrophy or atrophy of the testicles is diagnosed. In these patients a high risk of developing intraductal germinogenic neoplasia is reported, which transforms into invasive cancer within the next 10 years (Jorgensen et al. 1990).

15.1 Pathologic Anatomy and Way of Metastases

The morphologic classification of testicular cancer is based on the characteristics of the types of cells from which tumor develops, namely germinal or stromal cells. Germinogenic tumors (95%) develop from immature germinal cells and epithelium covering seminal ducts. Nongerminogenic tumors are neoplasms originating from hormone-producing cells and connective-tissue of the testicular coat.

They account for 5% of all testicular cancers. Germinogenic tumors are divided into seminomas and nonseminomas. Seminomas make up about one half of all testicular tumors. Tumors of the nonseminomatous type are divided into teratomas, choriocarcinomas and embryonal cell tumors (tumors of the vitelline sac). Embryonal carcinomas are more often observed in boys and remind embryonal carcinomas of the ovary in their structure. The morphological texture of teratoma is represented by two or more types of germ cell layers. The term “teratocarcinoma” refers to a mixed nonseminomatous form of testicular cancer, consisting of teratomatous components and those of embryonal cell cancer.

Seminomas usually are composed of cells of one and the same type, while non-seminomatous tumors may be both mixed, i.e. consisting of seminomatous and non-seminomatous components, and purely nonseminomatous. Mixed tumors make up about 40% of all germ cell tumors.

Tumors of the gonadal stroma make up 5% of all testicular cancers and are represented by Leydig cell tumor, Sertoli cell tumor and granulosa cell tumor.

The stages of the disease are distinguished according to the TNM classification.

The classification is used only for germinogenic tumors of the testicle.

Local spread of testicular cancer manifests itself with tumor invasion into the epididymis, spermatic cord and tunica of the testicle. It should be noted that the primary tumor lesion may be located in other organs or tissues, most often in the mediastinum and retroperitoneum. Extragonadal tumors develop as a result of aberrant migration of germ cells during embryogenesis or are formed from predecessor cells originating also cells of the thymus.

Lymphatic metastases occurs to retroperitoneal lymph nodes, more seldomly to inguinal, pelvic or mediastinal lymph nodes. The regional lymph nodes for the testicle are paraaortal, preaortal, interaortocaval, paracaval, precaval, retrocaval and retroaortal nodes. Intrapelvic and inguinal lymph nodes are considered as regional if operations on the stratum and inguinal area were previously done. In testicular cancers it is ipsilateral lymph nodes that are usually affected. Sometimes bilateral and cross-metastasis is observed conditioned by anastomoses between lymphatic vessels.

Hematogenic metastases are most often observed in the lungs, liver, brain and kidneys.

The earliest symptom of testicular cancer is appearance of tumor mass in the scrotum and tumescence of the scrotum. In some cases, tumor is not accompanied by symptoms until it reaches a large size. Usually the tumor is painless; however, with its growth, pain in the testicle and along the spermatic cord appears. In case of

hormonally active tumor, a change of secondary sexual characters is observed: appearance of gynecomastia, early puberty, hirsutism, etc. In 10% of cases the first symptoms of the disease, i.e. intensive drawing pain sensations in the area of the loin are conditioned by tumor metastases to retroperitoneal lymph nodes.

15.2 Methods of Diagnosis

Primary diagnosis of testicular cancer consists of examination and palpation of the stratum, inguinal lymph nodes, and mammary glands. Diaphanoscopy, X-ray examination of the stratum with a narrow light beam, permits to differentiate a non-transparent tumor from a cyst.

An important contribution to diagnosing germinogenic tumors of the testicle belongs to study of serum tumor markers – alpha fetoprotein (AFP), human beta-chorionic gonadotropin (b-CG) and lactate dehydrogenase (LDH). Higher level of AFP and/or b-CG is observed in about 90% of patients with nonseminomatous testicular tumors. However, the normal level of tumor markers does not exclude the disease (Albers et al. 2005). Determining the level of serum tumor markers helps diagnose testicular tumors at early stages, diagnose extragonadal germinogenic neoplasms and is of significant aid in discerning relapses and in refining prognosis.

Alpha-fetoprotein (AFP) belongs to the group of the oncofetal antigens and is a structural analog of albumen. In the embryonal period it is secreted in the vitelline sac, liver and gastrointestinal tract of the fetus. In the early stages of fetal development AFP replaces albumen and performs its transport functions. At the age over 1 year old, the upper limit of the norm of AFP concentration in blood serum corresponds to 15 ng/mL.

Germinogenic tumors containing elements of the vitelline sac are as a rule accompanied by a significant increase in AFP level. It should be remembered that increase in level of this marker may be observed in other diseases, such as hepatocellular cancer, tumors of the stomach, gallbladder, pancreas, lungs.

Human b-CG is a protein hormone synthesized by trophoblastic structures, the degree of increase in level of serum b-CG being proportional to the mass of tumor tissue (Matveev and Volkova 2003). The level of b-CG may increase also in the presence of neoplasms of the pancreas, liver, stomach, lungs, mammary gland and kidneys.

The value of lactate dehydrogenase in testicular cancer is not high but its increase by more than 2,000 U/L is a sign of tumor. Lactate dehydrogenase is an enzyme secreted by muscular tissue. The enzyme has five isomers, one of which is often produced by testicular tumors (Matveev and Volkova 2003). Lactate dehydrogenase reflects the degree of tissue destruction and is used for prognosing the course of the disease (Albers et al. 2005).

Ultrasonography (US) is of primary importance in diagnosing testicular tumors and in assessing the degrees of dissemination of tumor process. In order to obtain a distinct image of testicular tissue, it is recommended using a sensor with frequency

7.5 MHz. As a rule, tumor is represented by one or several hypoechoic foci. It is very difficult to correctly stage testicular cancer with US methods because of absence of distinct sonographic visualization of the tunica albuginea (Matveev and Volkova 2003). In case of seminoma, the exact stage of the disease according to the T category can be determined in 45% of patients, and it is only in 8% of cases that it can be identified in cases of nonseminomatous histological types of testicular cancer. It is necessary to administer sonography of the testicles if retroperitoneal tumor, metastases in the viscera without detected primary lesion or a high titer of specific tumor markers are observed in a young male (Albers et al. 2005).

CT is recognized as an informative method of visualizing metastatic foci. This method has virtually completely replaced X-ray contrast lymphangiography, widely used in the past for visualizing retroperitoneal lymph nodes. However, this examination does not permit the unambiguous differentiation of residual tumor tissue after chemotherapy from fibrous-necrotic masses and teratoma (Bosl et al. 2005).

MRI of the scrotum in testicular tumors shows sensitivity and specificity approaching to 95–100%. However, no significant advantages over CT have been observed in assessing the state of affected lymph nodes (Matveev and Volkova 2003; Albers et al. 2005).

15.3 PET Diagnosis

^{18}F -FDG PET is efficiently used both for detecting the primary lesion and for revealing a relapse, assessing dissemination and evaluating the efficiency of treatment in patients with testicular cancer (Hain et al. 2000; Horwich et al. 1992; Fernandez et al. 1994; McLeod et al. 1991; Albers et al. 1999). According to numerous studies, the standardized uptake value (SUV) depends on the histological type of the tumor and ranges from 2.2 to 12.2 (Cremerius et al. 1998; Wilson et al. 1995; Sugawara et al. 1999). High ^{18}F -FDG uptake is observed in patients with nonseminomatous testicular tumors, whereas radiopharmaceutical (RP) uptake by the tumor focus is much lower for diagnosing seminomas and teratomas (Badjorin et al. 1992). It should be noted that moderate ^{18}F -FDG uptake in testicular tissue is observed in healthy persons, especially those of young age. This phenomenon is accounted for by the process of spermatogenesis.

^{18}F -FDG PET is also successfully used for assessing the dissemination of metastatic lesion (Fig. 15.1). Hain et al. (2000) demonstrated a diagnostic advantage of the method in detecting metastases of testicular cancer over traditional radiologic techniques (Hain et al. 2000). However, in the study of Cremerius et al. (1998) the informative value of ^{18}F -FDG PET and CT proved to be the same (Cremerius et al. 1998). Small dimensions of metastatic foci are the source of false-negative PET results.

The advantage of ^{18}F -FDG PET over traditional methods of radiologic diagnosis in evaluating the efficiency of chemotherapy and radiologic therapy has been demonstrated in numerous studies, since it is PET that permits the differentiation of viable tumor tissue from post-radiation fibrosis or residual necrotic tissue after chemotherapy. In the study of Badjorin et al. (1992), according to CT data,

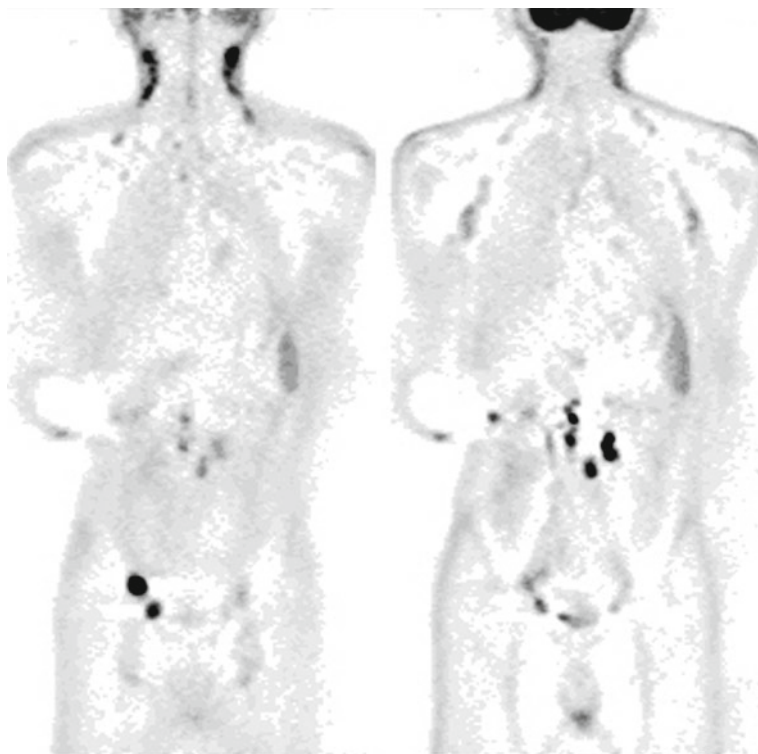


Fig. 15.1 ^{18}F -FDG PET of a patient with non-seminoma testicular cancer, after orchiectomy. Metastatic uptake in right inguinal and retroperitoneal lymph nodes

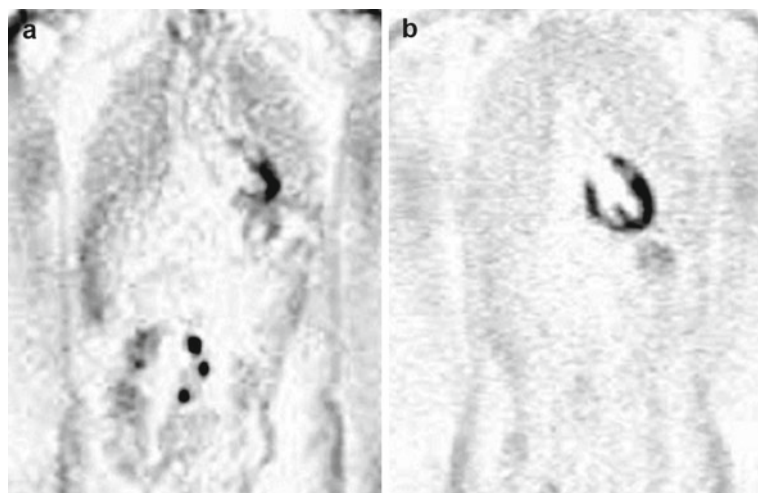


Fig. 15.2 ^{18}F -FDG PET. Efficiency evaluation of polychemotherapy in chorionembryonic testicular cancer metastases to retroperitoneal lymph nodes (a) before treatment, (b) after treatment. Metastases are not visualized after treatment

false-positive results were observed in more than 40% of patients, due to a solid mass persisting after therapy but not containing tumor elements (Badjorin et al. 1992). This group of patients underwent a surgical intervention in order to more precisely assess the presence of residual tumor tissue. ^{18}F -FDG PET permits solving this task in a noninvasive way. Cremerius et al. (1998) defined the accuracy of ^{18}F -FDG PET in evaluating the efficiency of polychemotherapy as 86%, while the accuracy of CT was only 59% (Cremerius et al. 1998). The same authors established the optimum term for implementing ^{18}F -FDG PET as 2 weeks after the end of a course of polychemotherapy (Fig. 15.2). Performing the procedure in earlier terms entails appearance of false-negative results. Administration of ^{18}F -FDG PET to patients with a biochemical relapse is necessary in order to determine the localization and dissemination of pathologic process. Sohaib et al. (2008) suggested the role of PET as the most appropriate imaging method for patients with raised tumor marker levels and negative radiologic imaging.

Thus, ^{18}F -FDG PET has a high diagnostic efficiency in detecting the primary lesion, and regional and distant metastases of testicular cancer.

The most promising application of PET seems to be its use for assessing the results of radiologic, surgical and chemical therapies, especially in difficult clinical situations: a high level of tumor markers, difficulty in differentially diagnosing between cicatricial tissue and continued growth, or between post-radiation necrosis and tumor relapse.

The use of traditional methods of radiologic diagnosis is based on the anatomic assessment of tumor volume, whose change occurs slowly, which causes difficulties in assessing tumor sensitivity to treatment. Alternatively, ^{18}F -FDG PET, even in the early stages (2–3 weeks) after the end of a course of therapy, permits the prediction of the efficiency of chemotherapy long before a decrease in volume of the neoplasm is detected by other methods. This is important in order to assess tumor resistance to therapy and to exclude the toxic effect of chemopharmaceuticals, as well as to choose another way of treatment.

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Currently it is accepted to distinguish among lymphoproliferative diseases the groupings of lymphomas, leukoses and lymphomas/leukoses (Gantsev 2004). Malignant neoplasms originating from the elements of lymph nodes or extranodal lymphatic tissue are qualified as lymphomas, while leukoses are tumors from peripheric blood cells, and the group of lymphomas-leukoses consists of diseases with both signs. Neoplasms of plasma cells, including myelomatosis and plasmocytoma, are not presently qualified as lymphomas.

Malignant lymphomas (MLs) are the most frequent form of lymphoproliferative diseases. Presently MLs constitute 5% of registered cases in oncologic morbidity. However, in recent years, a 3.9-times increase in this index has been observed. In most cases, MLs occur at the age of 16–40 years and have a chronic course. The disease is found in all countries, but currently some geographic regularities in epidemiology of certain kinds of lymphomas are established. For example, extranodal lymphomas localized in the oropharyngeal area are most often detected in Italy, primary lymphomas of the gastrointestinal tract are diagnosed in the Middle East. Endemic regions in equatorial Africa are described in which the biggest number of cases of Burkitt's lymphoma are registered (Gantsev 2004).

Statistical data of recent years show that 55–60% of ML cases are lymphogranulomatoses [Hodgkin's disease or Hodgkin's lymphoma (HL)]. HL is a primary tumor disease of lymphatic tissue, occurring unicentrally and disseminating by way of metastasis. The tumor substrate in HL, unlike other malignant neoplasms, consists of mature differentiated cells. Pathologic cells in the lymph node are clearly in the minority and are represented by Reed-Sternberg-Berezovsky giant cells, which are not diagnostically significant. The cellular composition includes both B-lymphocytes in different stages of maturation and T-lymphocytes with phenotype of T-helpers and T-suppressors. Such heterogeneity of tumor dictates the necessity of carrying out morphologic and immunohistochemical study of material, which permits detection of Reed-Sternberg-Berezovsky giant cells (Vazhenin et al. 2003).

Lymphoproliferative disease may develop in any organ or tissue where there are lymphoid cells (lymphoblasts, lymphocytes, follicular center cells – centrocytes

and centroblasts). Normally lymphoid cells are contained in lymph nodes, in the lymphatic pharyngeal ring (palatine tonsils, tonsils of the tongue, adenoids), thymus, aggregated lymphatic follicles (Peyer's plaques) of the small intestine, spleen and in extralymphatic organs (Gershanovich et al. 1995). The latter include brain, spinal cord, bone marrow, lungs, gonads, kidneys, gastrointestinal tract, skin, bones, uterus and tissues surrounding the eye-bulb (eye conjunctiva, lacrimal glands and soft tissues of the eye-socket).

The scientific literature indicates that considerable difficulty has long existed in drawing up the optimum classification of lymphoproliferative diseases which would satisfy both clinicians and pathomorphologists. However, the rapid development of molecular-genetic, immunomorphologic and biochemical methods of examination has facilitated the elaboration of a unified classification of lymphoid tumors (Table 16.1) by the experts of the World Health Organization (WHO). The assessment of tumor dissemination is done according to the Ann Arbor classification. It reflects the anatomic situation of pathologic foci relative to the diaphragm, number of affected regions, and the tumor affection of extralymphatic organs. Besides, in staging of the disease based on anamnestic data and on the results of physical examination, intoxication symptoms (fever, night pouring perspiration, loss of weight) are obligatorily taken into account, which permit to qualify a given case as belonging to A or B subgroups.

16.1 Methods of Diagnosis

The WHO has elaborated and endorsed an algorithm for examining patients with lymphoproliferative diseases, including obligatory and auxiliary diagnostic procedures. The obligatory procedures are: morphological study of the biopsy material, laboratory studies, X-ray of the organs of the thorax, CT of the thoracic and abdominal cavities and of the organs of the small pelvis. Additionally, all the patients undergo trepan biopsy. The auxiliary procedures include laparotomy with splenectomy, puncture biopsy of the liver, scintigraphy of the skeleton in case of marked pain syndrome in the bones, CT of the head and neck organs, gastroscopy or X-ray of the organs of the abdominal cavity in patients with suspected lesion of the gastrointestinal tract, MRI of the spine and cytological study of cerebrospinal fluid in patients with the fourth stage of the disease and meningeal symptoms (Gantsev 2004).

16.1.1 PET Diagnosis

16.1.1.1 Staging of Lymphoproliferative Diseases

The role ^{18}F -FDG PET in diagnosing lymphoproliferative diseases is very important. The method is widely used in staging of the tumor process, treatment efficiency evaluation, including early stages of therapy, making prognosis, radiotherapy planning and diagnosis of relapses (Buchmann et al. 2001; Carr et al. 1998; Fuster et al.

Table 16.1 WHO classification of the main forms of lymphoid neoplasms (1999)

Morphological and immunological tumor type	Nosological form
B-cell precursor tumors	• B-lymphoblastic lymphoma (acute B-cell lymphoblastic leukemia)
peripheral (mature) B – cell tumors	• Chronic B-cell lymphocytic leukemia (small lymphocyte lymphoma) • Plasma cell myeloma (plasmacytoma) • MALT extranodal B-cell lymphoma of the marginal area • Follicular lymphoma • Mantle cell lymphoma • Diffuse B-large cell lymphoma • Burkitt lymphoma
T – cell precursor tumors	• Acute T-cell precursor lymphoblastic leukemia
Peripheral (mature) T-cell tumors	• T-cell prolymphocytic leukemia • T-cell large-granular lymphocyte leukemia • Aggressive NK-cell leukemia • T-cell lymphoma (adult leukemia) • Extranodal T-cell lymphoma, nasal type • T-cell lymphoma with enteropathy • Hepatolienal T-cell lymphoma • T-cell panniculitis-like lymphoma of subcutaneous tissue • Mycosis fungoides • Peripheral T-cell lymphoma, unspecified • Angioimmunoblastic T-cell lymphoma • Anaplastic large-cell lymphoma with primary systemic lesion
Hodgkin's lymphoma	• Lymphoid predominance • Nodular sclerosis • Mixed-cell variant • Lymphoid exhaustion

2006). The obtaining of a whole-body image in PET is the main advantage of the method. Within a single examination it is possible to assess lymph nodes of virtually all the anatomic regions as well as spleen and simultaneously to analyze the state of extralymphatic organs (Fig. 16.1). In this process the size of lymph node does not have importance. Meanwhile, the assessment of diagnostic accuracy of the method is in some cases difficult due to the absence of a “gold standard” to which visualizing abilities of PET could be compared. As a result, some pathological foci still remain without tissue verification (Abozied et al. 2005; Barnnigton and O’Doherty 2003). In some cases dynamic observation of patients may help find tumor foci detected in PET. If changes detected in PET are of great significance in determining the stage of disease, retrospective data revision obtained by other methods of radiological visualization. Such an approach can ensure correct staging and in 25–40% of cases it can permit restaging of the disease (Schiepers et al. 2003).

According to different authors, PET sensitivity may reach 100% in diffuse B-cell lymphoma, 98% in Hodgkin's lymphoma and follicular lymphoma, 67% in lymphomas of the pallium area, 40% in peripheral T-cell lymphoma 95% in myelomatosis. In MALT lymphomas of the gastrointestinal tract this value usually does not exceed 57–64% (Beal et al. 2005; Buchmann et al. 2001; Elstrom et al. 2003; Fnedberg et al. 2004; Gambhir et al. 2001; Jerusalem et al. 1999). According to Schiepers (2003), such data spread of the index of sensitivity in diagnosing different morphological types of lymphomas may be conditioned by the histological type of neoplasm and degree of malignancy of tumor cells (grade). However, some research results contradict this statement. For example, Schoder et al. (2005) compared standardized uptake values (SUVs) in indolent and aggressive non-Hodgkin lymphomas

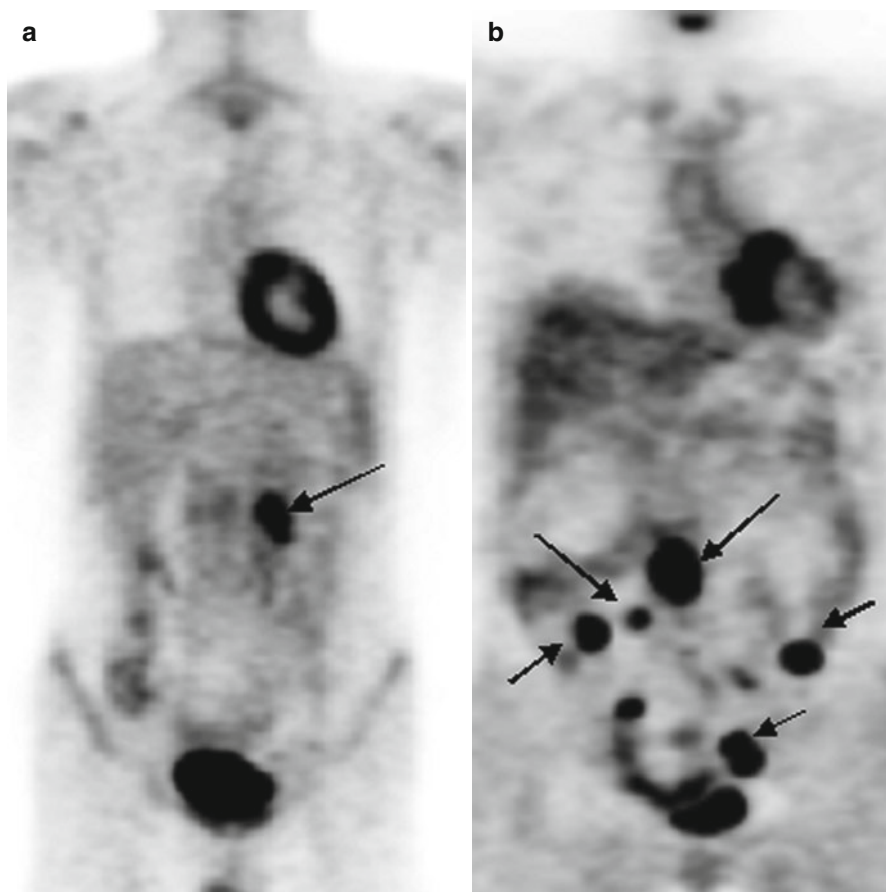


Fig. 16.1 ^{18}F -FDG PET of patients with various stages of LGM and NHL. (a) solitary pathological uptake of the retroperitoneal lymph nodes; (b) pathological uptake of intra- and retroperitoneal lymph nodes; (c) pathological uptake of mediastinal and right axillary lymph nodes and of the spleen; (d) pathological uptake of mediastinal lymph nodes, of the right humeral bone, of Th11, rib and right iliac bone

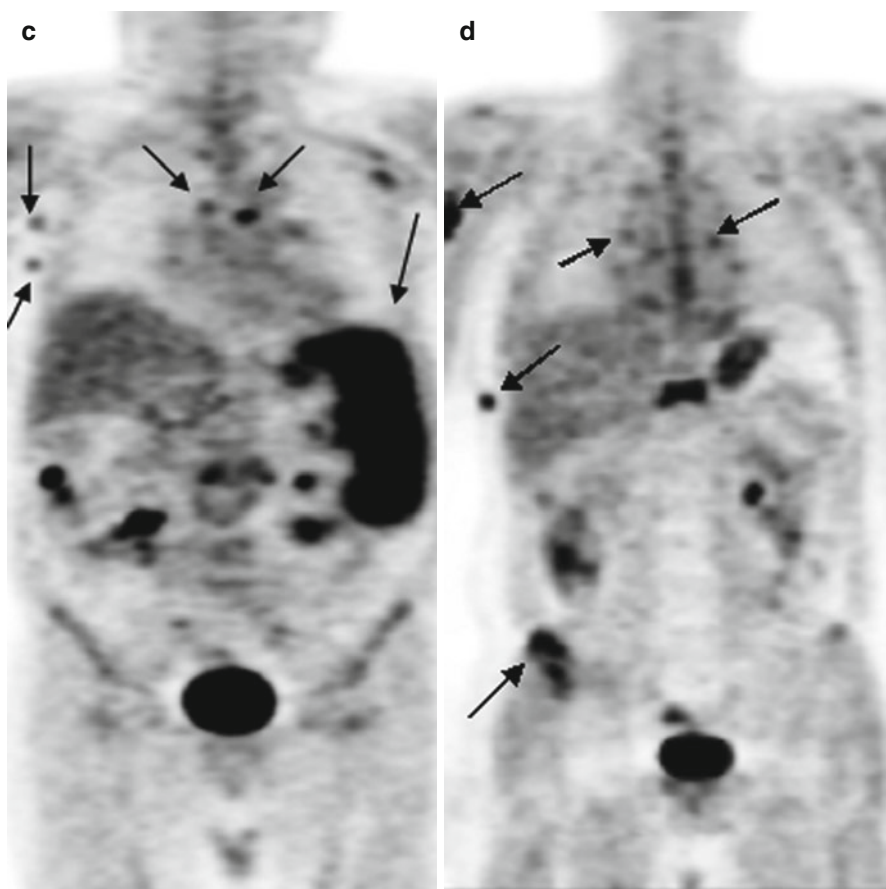


Fig. 16.1 (continued)

(NHLs). According to them, the SUVs were significantly higher in aggressive lymphomas. At the same time, PET sensitivities for lymphomas with indolent or aggressive courses differed only slightly and were 81% and 83% respectively. In this context the authors think that SUVs do not influence the sensitivity of the method. At the same time, the specificity of PET data in the presence of high SUVs grow significantly. These results are confirmed by other researchers who also ascertained high sensitivity of the method with indolent NHL. In particular, they observed a high ^{18}F -FDG uptake in malignant cells of follicular lymphoma, which in most cases is characterized by relatively benign course (Blum et al. 2003; Jerusalem and Beguin 2002, 2005).

High diagnostic accuracy of ^{18}F -FDG PET in the staging of malignant lymphomas has been demonstrated by many authors (Moog et al. 1997; Pakos et al. 2005; Schiepers et al. 2003; Talbot et al. 2001; Vinnicombe and Rezneck 2003). It has been observed that informative value of PET is higher by 15–25% than that of CT.

Fig. 16.2 ^{18}F -FDG PET of a patient with follicular lymphoma and pathological uptake in lymph nodes on both sides of the aorta, of the axilla and of the spleen and of bone marrow



In this context most researchers are of opinion that PET should become a routine method of radiological visualization in patients with lymphoproliferative diseases. According to some data, the efficiency of detecting malignant lesion of the bone marrow by means of ^{18}F -FDG PET is considerably higher than that of trepan biopsy (Isasi and Blaufox 2005).

The most frequent sources of false-negative results in trepan biopsy is locality of malignant process in the bone marrow and operative problems arising in obtaining a small volume of tissue. In order to determine PET efficiency in diagnosing malignant lesion of the bone marrow, Pakos et al. (2005) implemented metaanalysis of 13 published research works. In their opinion, PET sensitivity in detecting malignant lesion of the bone marrow in patients with lymphomas varied within the range of 52–95%, and specificity ranged from 67% to 89% (Fig. 16.2). The highest PET sensitivity (up to 76%) was observed in Hodgkin's lymphoma, diffuse large-cell lymphoma and Burkett's lymphoma. In follicular lymphoma, lymphoma of the pallium area, MALT lymphoma and small lymphocyte lymphoma, the sensitivity index did not exceed 30%. In this context the authors think that the probability of obtaining false-negative results in PET in diagnosing malignant lesion of the bone marrow significantly increases in patients with indolent lymphomas. According to some

data, ^{18}F -FDG PET sensitivity in detecting malignant lesion of the spleen exceeds twice that of CT and reaches 100%. However, the specificity of the two methods is virtually the same at 57% (Jerusalem 2005). Meanwhile, the data of other authors indicate that the specificity of PET in diagnosing malignant lesion of the spleen is 1.5-times as high as that of CT and constitutes 89% (Isasi and Blaufox 2005). Comparison of the results of scintigraphy with PET data in assessing the bone system showed that the sensitivity of both methods is approximately similar, being 87% and 89% respectively. However, PET specificity is significantly higher than that of scintigraphy and constitutes 91% (Moog et al. 1999).

The reported data confirm a high informative value of ^{18}F -FDG PET in diagnosing malignant lymphomas. At the same time, it is still obviously necessary to continue studying and detecting factors influencing the intensity of radiopharmaceutical (RP) uptake in tumor and in intact tissues, and consequently the specificity of the obtained results. In particular, high ^{18}F -FDG uptake may be observed in a number of benign changes (Abozied et al. 2005). The most frequent causes of this phenomenon are reparative processes in the area of operative interventions, including biopsy sites, as well as inflammatory changes in lymph nodes and extralymphatic organs (reactive lymphadenitis, sarcoidosis, tuberculosis, pneumonia). Physiological RP uptake may be observed in the thymus in consequence of its benign hyperplasia after polychemotherapy. These PET signs may persist for 6–12 months, especially in children before 14 years of age (Fig. 16.3). There are cases of high ^{18}F -FDG uptake in the bone marrow of patients with expansion of hemopoiesis during the first 3–4 months after the end of polychemotherapy and in patients receiving colony-stimulating factors or those who underwent bone marrow transplantation. However, determining the non-tumorous nature of bone marrow lesion in PET is not, as a rule, a difficult task. Benign hyperplasia of the bone marrow is characterized by diffuse symmetric uptake of RP and low SUVs. In case of tumor invasion of the bone marrow, unilateral local uptake with high ^{18}F -FDG uptake is characteristic. In order to exclude false-positive results in the area of the radiation field and adjoining organs and tissues, PET examination should be implemented 2–3 months after radiotherapy. In this process an area of moderately high RP uptake can be observed whose anatomic boundaries correspond to the radiation field.

Physiological RP uptake in brown fat situated along the skeletal muscular system is a frequent factor impeding the interpretation of PET data. In this situation it is not possible to assess the state of lymph nodes of the neck, supraclavicular areas and superior aperture of the thorax. Special patient preparation for examination in some cases may improve the quality of the obtained image. Most often, young and asthenic patients are recommended to put on warm clothes with a thick collar, best of all of wool, on the examination day. Also, 20 min before RP injection the patient is positioned in the treatment room under a wool blanket. Some authors suggest taking benzodiazepine or phenozepam 24 h before the examination (Naumann et al. 2004).

The fused images of PET/CT even with only low-dose CT may enable the differentiation between lymph node activity and physiologic uptake in brown fat tissue especially in the cervical region and upper thoracic aperture. It is clear that the careful analysis of PET images, anamnestic, clinical and laboratory data, study of the

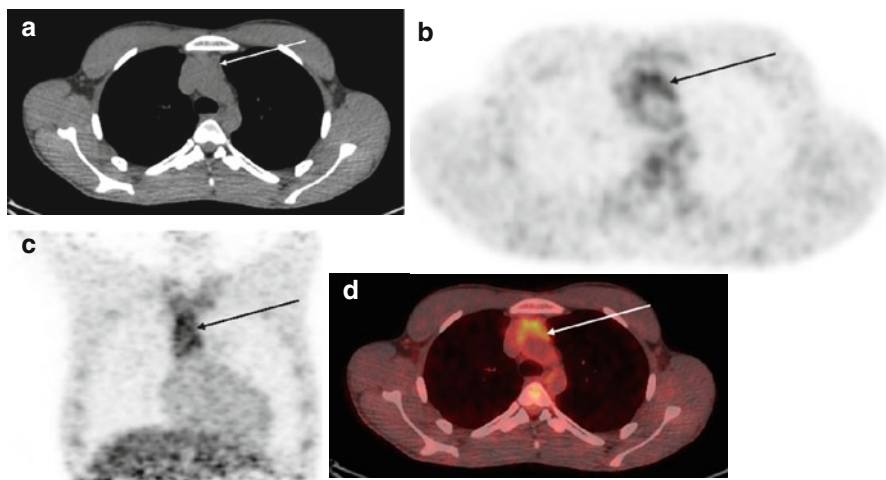


Fig. 16.3 ^{18}F -FDG PET/CT of the patient with LGM after 4 courses of polychemotherapy. CT (a) demonstrate an anterior mediastinal mass. Physiologic FDG uptake is seen in hyperplastic thymus on PET (b, c) and PET/CT (d)

results of other methods of radiological examination and correct patient preparation for examination permit in most cases the avoidance of false-positive results.

16.1.1.2 Treatment Efficiency Evaluation and Disease Prognosis

The speed of tumor reaction to therapy is one of the main factors conditioning disease prognosis. Now it has been proved that longer remissions are observed in patients with early complete metabolic response (after two to three courses) after the start of therapy. Besides, the possibility of early prognosis of therapy efficiency permits modification of the treatment (Tonzuka et al. 2004). In case of good tumor response to treatment, a decrease in SUV is observed as soon as on the 2nd to 5th days and persists until the end of treatment. ^{18}F -FDG PET sensitivity varies within 79%, its specificity is 92% and its diagnostic accuracy is 85% (Jerusalem 2005; Juweid et al. 2005; Mikhael et al. 2000, 2005; Rigacci et al. 2005).

Kostakologlu et al. (2002) performed PET in patients with malignant lymphomas after the first cycle of polychemotherapy and at the end of chemoradiotherapy. In doing this correlation between PET results and progression-free survival rate was higher after the first cycle of the polychemotherapy than at the end of chemoradiotherapy. The amount of false-positive data after the first cycle made up 15%, while after the end of chemoradiotherapy it was 35%.

In order to study the prognostic role of the method, Mikhael et al. (2005) performed PET after 2–3 courses of polychemotherapy. According to them, the progression-free 5-year survival rate was higher in patients with complete metabolic tumor response to therapy and constituted 89%. At the same time, in patients with partial regression of malignant neoplasms this index was defined as 59% and in patients with metabolic progression it did not exceed 16% (Fig. 16.4). In this context the

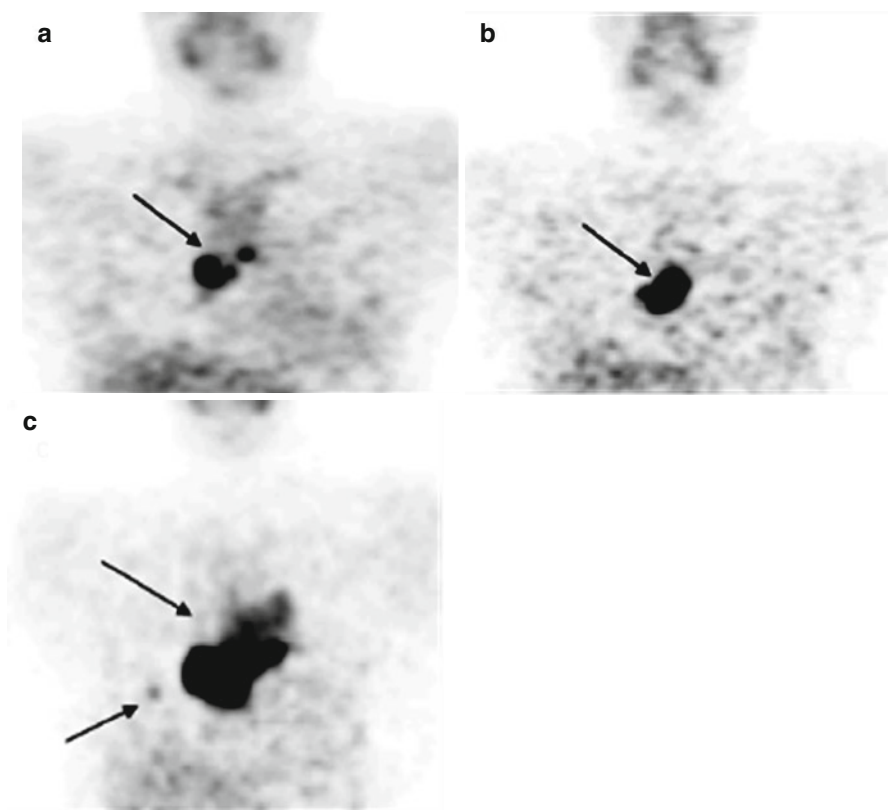


Fig. 16.4 ¹⁸F-FDG PET in a patient with LGM and increasing uptake. (a) before treatment. (b) after two courses of polychemotherapy. (c) after the end of polychemotherapy. No evidence of therapy response

authors think that SUVs are a reliable prognostic factor of the course of lymphoproliferative disease.

Achieving the complete remission of disease is the main goal of any treatment. However, structural imaging methods (US, CT, MRI) do not always permit to confirm or refute remission. This is usually due to differential diagnostic difficulties arising in discriminating between tumor lesion and sclerotic changes. As a result, in 30–60% of cases patients are wrongly diagnosed with unproven remission or relapse. According to different authors PET sensitivity in diagnosing relapses varies within the range of 71–100%, specificity is from 69 to 100%, the positive prognostic value of the method is 80–100% and negative prognostic value is 93% (Panizo et al. 2004; Partridge et al. 2000).

Overall, the data show that PET permits the identification of patient groups with high risk of relapse early after the start of polychemotherapy. This will facilitate timely transfer of patients to high-dose therapy. At the same time, identification of

patients requiring less intensive treatment can decrease the percentage of complications, including mortality caused by early and late toxic reactions.

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Melanoma is a relatively rare malignant tumor. Its share among all the oncological diseases makes up only 1.0–1.5%. However, for the last 10 years a steadfast tendency toward increased melanoma incidence has been observed in the Russian Federation. For example, in 1997 the intensive morbidity index constituted 2.93 per 100,000 of population. By 2007 it corresponded to 4.55 per 100,000 population. So, the index increment made up 4.96% (Merabishvili 2006).

Skin melanoma develops in people over 30. In most cases melanoma develops in the site of a pigmented nevus or birthmark. Nevi appear in childhood; they increase in size with growth of the organism and as a rule stop their growth after the puberty period. Subsequently birthmarks usually undergo depigmentation and fibrosation. Among the factors contributing to malignization of nevi, there are high insolation, different traumas, as well as endocrine and genetic factors (Gantsev 2004).

The clinical picture of melanomas is extremely diverse. Tumors may have different forms, colors, consistency and situation. The dimensions of a malignant neoplasm may vary from several millimeters to many millimeters, but most often they do not exceed 1–3 cm in the maximum dimension. Melanoma may have a round, oval, triangular, polygonal and any other form. The tumor surface may be unchanged, moist or ulcerous, slightly bleeding, or it may be covered with crusts. Skin pattern disappears on the surface of melanoma. The consistency of pathological formation is usually dense, or more seldom elastic. The form of melanoma in this case may be tuberous, nodal, hemispherical or fungiform. Tumor pigmentation has an uneven character of pigment distribution. Several colour combinations may be observed within the same tumor. Melanoma may have different colours – brown, black, blue, pink, violet; but it may be unpigmented as well. There are a number of clinical signs whose occurrence suggests the necessity of advanced patient examination in order to exclude skin melanoma. According to A.I. Paches, they are:

1. Change in colour of the nevus, its sharp pigmentation (up to a black colour), and in some cases decrease in pigmentation
2. Uneven coloring
3. Changed or completely absent skin pattern, desquamation of the nevus
4. Appearance of an inflammatory areola around the nevus (corolliform redness)

5. Changed peripheric configuration; for example, blurred contours of the nevus
6. Increase in size and density of the birthmark
7. Appearance of small nodulous papillomatous elements with necrosis foci at the base of the nevus
8. Appearance of itch, burning, pricking and tension in the area of the nevus
9. Appearance of fissures, ulcers and hemorrhage

17.1 Pathological Anatomy and Mechanisms of Metastases

Currently the neuroectodermal theory of tissular genesis of skin melanoma is most widely recognized. The tumor consists of melanocytes or of nevus cells situated in the basal layer of the epidermis along the dermoepidermal interface. Their main function is synthesis of the melanin pigment, which is taken up and accumulated by epidermal cells.

It is accepted to distinguish three main types of skin melanoma: superficial spreading, nodular and acral-lentiginous melanomas. Two phases are distinguished in melanoma: the horizontal phase, when the disease spreads within the epithelial stratum, and the vertical phase, when malignant cells penetrate into superficial layers of the epidermis with invasion of the basal membrane of the derma and hypodermic fatty tissue. The horizontal phase of superficial spreading melanoma lasts for up to 7 years, while that of acral-lentiginous melanoma lasts for 10–20 years. The vertical phase as a rule is characterized by rapid tumor growth and tendency to metastasis.

In 60% of cases it is superficial spreading melanoma that is observed. Initially it looks like a black or brown pigment spot with diameter no larger than 0.5 cm that does not rise over skin surface. In the vertical phase, heavy tumor growth with formation of an exophytic component takes place. Nodular melanoma is observed approximately in 20% of cases, it is in the form of a node, fungus or polyp of a black or blue-red color. Acral-lentiginous melanoma accompanies Dubrey's melanosis and constitutes 20% of all skin melanomas. The horizontal phase of pathological formation is long and transition of lentigo to lentiginous melanoma occurs gradually. During malignant transformation, a lentigo acquires an irregular form with scalloped contours and uneven pigment distribution.

Melanomas metastasize by the lymphogenic route to skin and lymph nodes, and by the hematogenic route to the liver, lungs, brain, bones, kidneys and adrenal glands. The tendencies of the tumor process disseminating depend upon the biological characteristics of a given pathological formation. Some forms are observed which metastasize for a long time only lymphogenically to regional lymph nodes. At the same time, there are melanomas with high malignancy potential, with a tendency to early hematogenic dissemination. Forms of melanomas which metastasize to the skin should be particularly stressed. Among them there are satellite, nodular, erysipeloid and thrombophlebitis-like forms. Satellites are multiple small eruptions situated near the primary focus or at some distance from it in the form of spots retaining the color of the tumor. The nodular form of skin metastases manifests

itself as multiple subcutaneous nodes of different size, which may be situated at any distance from the primary formation. The erysipeloid form of skin metastases looks like an area of bluish-red edematous skin surrounding the tumor. The thrombophlebitis-like melanoma manifests itself by radial spreading, painful hardening, enlarged superficial veins and skin hyperaemia around the tumor (Vazhenin et al. 2003).

17.2 Methods of Diagnosis

Diagnosing skin melanoma presents some difficulty. At the beginning of the disease there is no distinct clinical picture, and consequently tumor is hard to distinguish from benign pigment formations. In diagnosing skin melanoma, data of visual examination, palpation, and radioisotopic, thermometrical and morphological methods of examinations are used.

When visually examining a cutaneous covering, it is preferable to use a magnifying glass. Both the tumor itself and the whole skin surface should be examined in order to exclude primary multiple melanoma. The form, size, colour of the tumor and integrity of the epidermis over it are visually assessed.

The primary tumor, surrounding soft tissues and all the lymph nodes available for examination are subjected to palpation. It is necessary in order to determine tumor consistency and the degree of its displacement relatively to subjacent tissues as well as to detect transient, regional and distant metastases of melanoma. Secondary changes in the skin have even edges, round form and dense elastic consistency. Lymph nodes affected by melanoma metastases are enlarged and assume a dense consistency.

Radioisotopic examination is done with twice-substituted sodium phosphate labeled with radioactive phosphorus. The substance is introduced orally on an empty stomach and then radiopharmaceutical (RP) uptake into the tumor and that in the symmetric area of healthy skin are compared by way of contact radiometry. According to some data, RP hyperfixation over a melanoma is four-times as high as that over the contralateral intact area of the epidermis.

The thermometric method is intended for detecting pathologic processes accompanied by local skin temperature change relative to the healthy area. Values of the temperature gradient exceeding 1° attest to the malignant character of pathological formation, while those lower than 1° confirm its benign nature. Superficial spreading and nodular melanomas are hyperthermic. Difference in temperatures in the tumor and in normal tissues may reach 4° . In melanoma the thermometric and histological diagnoses coincide in 95% of observations, while in case of benign neoplasm they do in 70% of cases.

The morphological examination is decisive in diagnosing skin melanoma. Impression smears are taken for cytological examination by applying a defatted slide to the moist or ulcerous surface of melanoma. If the neoplasm is covered with crusts, tissue moistened with neutral fat is applied to it 1–2 days before the examination and then crusts are easily removed without injuring the tumor. The cytological analysis coincides with the histological one in 97% of cases. Excisional biopsy is

absolutely contraindicated in melanoma due to the danger of dissemination of the tumor process.

Staging of the tumor process is done by means of radiological methods of diagnostics: US, CT and MRI (Edge et al. 2010). The diagnostic accuracy of these methods in detecting metastatic lesion of regional and distant lymph nodes is roughly the same and constitutes 47–75%, and 78–93% in case of the liver (Tyurin 2007).

For diagnosing metastatic lesion of lymph nodes before the operation mapping of sentinel lymph collectors is currently widely used. Some amount of microfiltered technetium-labeled sulfur colloid is introduced subcutaneously around the primary formation. Particles of this substance spread through lymph collectors and accumulate in the affected lymph nodes, which can be detected with the help of a gamma camera. According to some data, the sensitivity of this method reaches 100% and its specificity is 97% (Vazhenin et al. 2003).

17.3 Staging

Currently the clinical and pathological TNM classifications are used for staging of melanoma. They consider the criterion of the depth of tumor invasion into the dermis suggested by Clark in 1969 and that of tumor thickness developed by Breslow in 1970.

17.3.1 PET Diagnostics

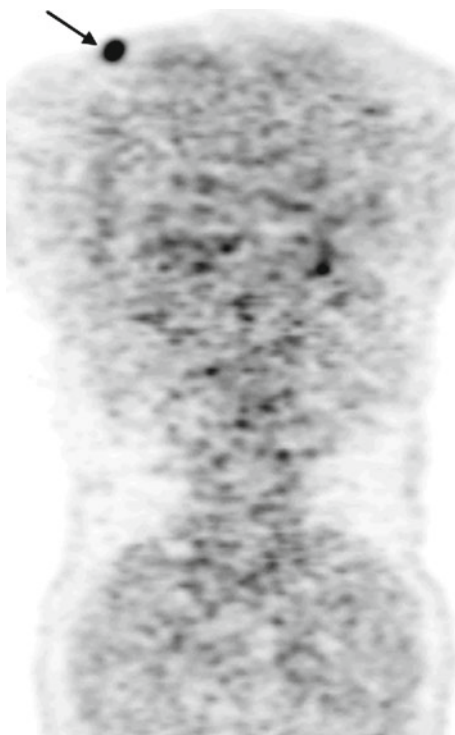
17.3.1.1 T Category

Currently there are no data on the informative value of ^{18}F -FDG PET in diagnosing primary melanoma formations. This is due, first of all, to the fact that the disease manifests itself with a skin lesion and is therefore available for non-invasive visual examination. Besides, the small dimensions of the primary focus are usually beyond the scope of PET's resolving capacity. Meanwhile, invasion of more than 4 mm implies the highest stage of the disease (T4). Among the studies of recent years, there are very few publications devoted to detecting the primary focus in skin melanoma patients (Damian et al. 1996; Gershenwald et al. 2000; Jadvar et al. 2000). In addition, the size of the neoplasm in all the described cases exceeded 2–4 cm (Fig. 17.1).

17.3.1.2 N Category

The diagnostic accuracy of PET in detecting metastatic lesion of the regional lymph nodes directly depends on the stage of the tumor process according to T category. For example, PET sensitivity in T1 and T2 stages does not exceed 17%, while in T3 and T4 it may reach 92% (Boni et al. 1995). This is mainly due to the small quantity of tumor cells contained in the affected lymph node. This leads to ^{18}F -FDG isometabolism in metastatic foci (Acland et al. 2000; 2001; Blessing et al. 1995; Macfarlane et al. 1998; Mijnhout et al. 2002; Wagner et al. 1997).

Fig. 17.1 ^{18}F -FDG PET of a patient with skin melanoma. In the right scapular region a focus of pathological FDG uptake is detected



17.3.1.3 M Category

Skin melanoma is one of the few diseases to be distinguished by unpredictable and often unexpected ways of metastasis. For example, melanoma metastases can be detected not only in the distant lymph nodes, liver and lungs but also in such uncommon organs as the spleen, gallbladder, skin and hypodermic fatty tissue. In this context, implementing whole-body PET examination is not only a suitable but also a necessary means of efficient staging of the tumor process. The diagnostic accuracy of ^{18}F -FDG PET in detecting metastatic foci ranges within 88–98%, depending on their anatomic situation (Balch et al. 2001; Delbeke 1999; Eigtvad et al. 2000; Holder et al. 1998; Wagner et al. 1999).

17.3.1.4 Treatment Efficiency Evaluation

PET is a highly informative radiodiagnostic method for the restaging of melanoma and may be efficiently used in dynamic control over patients after surgical interventions. PET permits the detection of additional metastatic foci in 20–30% of patients with skin melanoma in the postoperational period and in 10–135 of cases to reveal signs of relapse in the area of the cicatrice. For this reason, in some clinics abroad PET has completely replaced CT and currently is an obligatory method of radiodiagnosis in skin melanoma patients (Krug et al. 2000; Paquet et al. 2000; Rinne et al. 1998; Steinert et al. 1995; Tyler et al. 2000; Mijnhout et al. 2003).

Thus, the role of ^{18}F -FDG PET in diagnosing primary formation in melanoma patients still remains undetermined. At the same time, the method shows high diagnostic accuracy in staging and restaging, and in treatment efficiency evaluation.

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18.1 Epidemiology

Malignant tumors primarily originating from osseous and muscular tissue are a relatively rare disease (0.6% of the total number of oncological diseases). These tumors have a very heterogeneous structure, diverse histological texture and different degrees of malignancy. The frequency of soft tissue (muscle) tumors in epidemiological reports is 2–3 per 100,000 people and that of primary bone tumors is 1 per 100,000. About 780 soft tissue sarcomas of different localizations and 2,600 tumors of bone tissue are reported every year in the USA (Landis et al. 1999).

Sarcomas of soft tissues or soft tissue tumors (STT) may have any localization, though it is mainly limb muscle bulk that is affected. For some kinds of tumors, age criteria have some importance. For example, rhabdomyosarcoma appears mainly in children, whereas fibrohystiocitoma or liposarcoma appear at an elderly age. The same distribution characterizes primary bone tumors: osteosarcoma or Ewing's sarcoma as a rule develops at an adolescent age, contrary to chondrosarcoma which develops at an elderly age.

Most muscle and bone tumors do not have a distinct etiology. However, recently there have been data on special forms, in which typical (for a given form) gene mutations and tumor suppressor genes have been found. For example, RB and p53 are often revealed exactly in presence of sarcomas (Golubovskaya et al. 2008).

Soft tissue sarcomas are malignant tumors which emerge in the mesenchyma. Bone tumors are classified according to the dominant cytosignal: 20% of tumors have the so-called chondral differentiation, in 40% of cases they issue from the hemopoetic system (multiple myeloma), in 18% they primarily originate from bone tissue, and in 4% they are of fibrohistiocytic origin. The histologic differentiation of Ewing's sarcoma is unknown (hypothetically it may be of mesenchymal origin).

18.1.1 The Degree of Malignancy of Tumors

1. Highly differentiated
2. Intermediately differentiated
3. Lowly differentiated
4. Non-differentiated

The operative classification of soft tissue tumors and primary bone tumors is given in Table 18.1.

Soft tissue and bone tissues metastasize hematogenously mainly to the lungs and to bone structures.

18.2 Diagnosis

The standard methodology of radiological examination includes roentgenography, CT, MRI, osteoscintigraphy and angiography. For final verification of the diagnosis, histological analysis is usually needed. For this purpose, open biopsy or bone marrow biopsy are done.

Table 18.1 STT and PBT classification

Description of tumor	Frequency of occurrence (%)	Typical age of manifestation (years)	Primary localization
Fibrosarcoma	10	30–50	Limbs
Malignant fibrohistiocitoma	20–30	50–70	Upper limbs, retroperitoneum
Lyposarcoma	15–18	40–60	Lower limbs
Leiomyosarcoma	7	50–60	Retroperitoneally, skin, subcutaneously
Rhabdomyosarcoma	14	7–11	Limbs, head, neck
Angiosarcoma	1	50–70	Skin, lower limbs
Synovial sarcoma	8–10	20–30	Articulations
Malignant schwannoma	5–10	25–50	Lower limbs, torso
Primary neuroectodermal tumor	1	15–35	Lower limbs
Extra skeletal Ewing's sarcoma	1	10–30	Lower limbs, paravertebrally in the thorax
Osteosarcoma	24	10–20	Tubular bones
Chondrosarcoma	13	30–60	Torso, limbs
Malignant large cell sarcoma	0.5	20–40	Epiphyses
Fibrosarcoma	3.3	15–60	The whole body
Histiocytoma	1.6	10–70	Tubular bones
Ewing's sarcoma	6.6	10–20	Skeleton
Primary bone lymphoma	6.6	20–70	Skeleton
Plasmocytoma	40	40–70	Head, backbone, pelvis, upper limbs

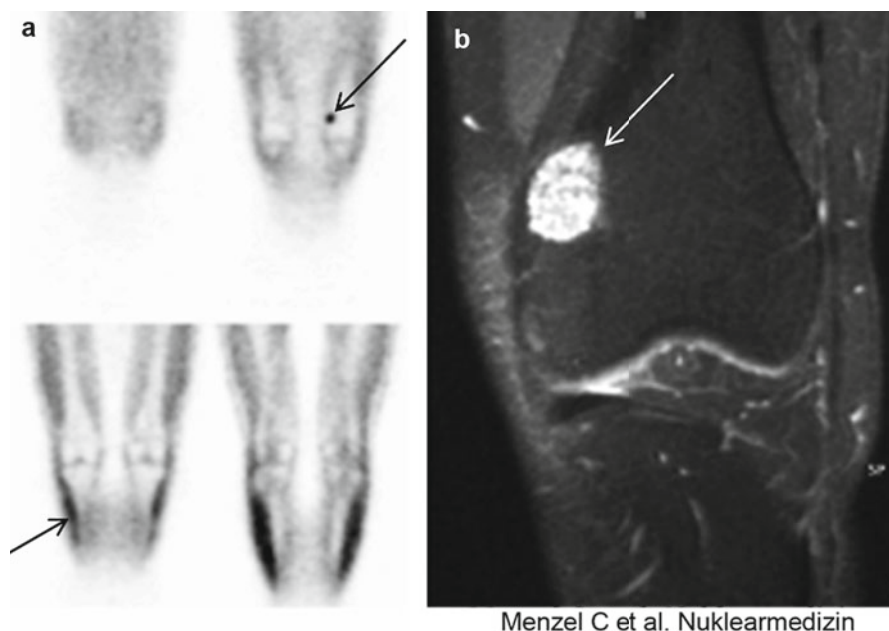


Fig. 18.1 ^{18}F -FDG-PET (a) and MRI with contrast enhancement of the lower limb chondroma. Pathological FDG uptake focus in the tumor (arrow) and symmetrical stress induced uptake in the lower limb muscles (arrows). Pathological contrast enhancement on the MRI image in the same position

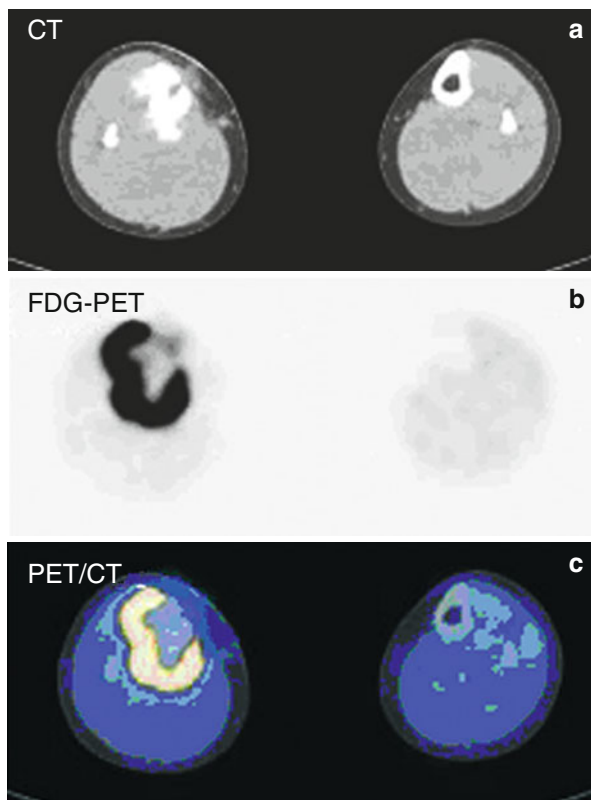
Currently PET in bone tumors does not have a definitely confirmed clinical significance, according to the data of the German Consensus, because of strongly uncoordinated research material (Zaplatnikov et al. 2003).

However, when summarizing the clinical experience and research of many leading clinics, one can positively affirm that ^{18}F -FDG PET-CT is the optimum method for diagnosing locomotive system diseases in routine diagnosis in centers specializing in bone system tumors (Figs. 18.1 and 18.2) (Kole et al. 1997; Lucas et al. 1998; Hain et al. 1999; Schwarzbach et al. 1999; Stokkel et al. 2001).

18.2.1 Methodology of Examination

Whole-body PET-CT scan includes the region of the primary tumor and the areas of possible primary metastasis (lungs, close bone structures) and embraces the whole body from the top of the head to the tips. CT with 2.5-mm steps (width of the section) and contrast enhancement. PET: diagnostic ^{18}F -FDG dose is 350 MBq, scanning is started 1 h after radiopharmaceutical (RP) introduction, time of scanning being 5 min per position, 5–7 positions, in all 25–35 min for an examination including limbs.

Fig. 18.2 ^{18}F -FDG-PET-CT. Primary bone sarcoma of the right shin bone. (a) Determining local dissemination by CT data is not possible due to the vagueness of the boundary between the tumor and healthy tissues. (b) ^{18}F -FDG-PET does not permit to determine the precise localization of the pathological focus. (c) Fused ^{18}F -FDG-PET-CT –image accurately reflects the extension and localization of the tumor



18.3 Staging for Evaluating Malignancy Degree

There is a direct correlation between ^{18}F -FDG uptake and the degree of malignancy of the primary tumor as well as its proliferative activity, mitosis rate and expression of the carrier protein, GLUT1, responsible for trans-membrane transfer of ^{18}F -FDG (Tateishi et al. 2006).

The correlation between the degree of malignancy and the standardized uptake value (SUV) is not still thoroughly explored since the inflammatory component present in aggressive benign tumors often induces false-positive results (Schuetze et al. 2005).

In a study by Franzius et al. (2002), a model of half-qualitative evaluation is suggested, based on the ratio of tumor/normal tissue (T/NT). When the value of the ratio is above 3, tumors are estimated as malignant; when it is lower than 1.5, they are considered as benign. The sensitivity of the method in bone tumors was 93%, its specificity being 66%; in soft tissues these values were respectively 97% and 66%.

The PET-CT combination provides good results also in diagnosing distant metastases to lungs and to bones (98% sensitivity and 100% specificity for lungs) (Franzius et al. 2002).

Examination of patients with STT and primary bone tumors (PBT) showed that the maximum SUV for the tumor before the onset of therapy correlates with the general survivability and to disease prognosis. A high SUV is observed in osteosarcoma, which is associated with a bad prognosis (Brenner et al. 2004).

18.4 Therapy Control

Early tumor response to non-adjuvant therapy is usually evaluated for planning further treatment and for prognosis estimation. Numerous works describe a decrease in RP uptake under chemotherapy. An important factor in such cases is provided not only by the decrease in RP uptake but also by contrast-enhanced CT data. When using both methods it becomes possible in 90% of cases to differentiate patients with a response to therapy from those in whom it is inefficient; when only one method is used, such a differentiation is possible only in 44% of cases (Nakamoto et al. 2005; Gayed et al. 2004).

18.5 Indications for ^{18}F -FDG PET-CT

18.5.1 Initial Staging

PET and PET-CT with ^{18}F -FDG may be the tool of first choice for highly sensitive primary diagnosis in order to evaluate local tissue lesion, reveal satellite foci and distant metastases (Fig. 18.3). The intensity of ^{18}F -FDG uptake by the tumor mass reflects the aggressiveness of the primary tumor. Semi-qualitative analysis, e.g., SUV, plays an important role here.

18.5.2 Treatment Efficiency Evaluation Restaging

^{18}F -FDG PET-CT is very successfully used for treatment efficiency evaluation and for tumor restaging. Basing on routine methods of examination, it is often difficult to differentially evaluate the local state of tissues after treatment that is to discriminate the viable residual tumor from post-operational and post-radiation cicatricial alterations. In such cases, early relapse detection is possible based on PET-CT data. This information has a high prognostic value and may cardinally change further management of the patient (a changeover to high-dose chemotherapy or radiotherapy in the presence of viable residual tumor even in the minimum volume).

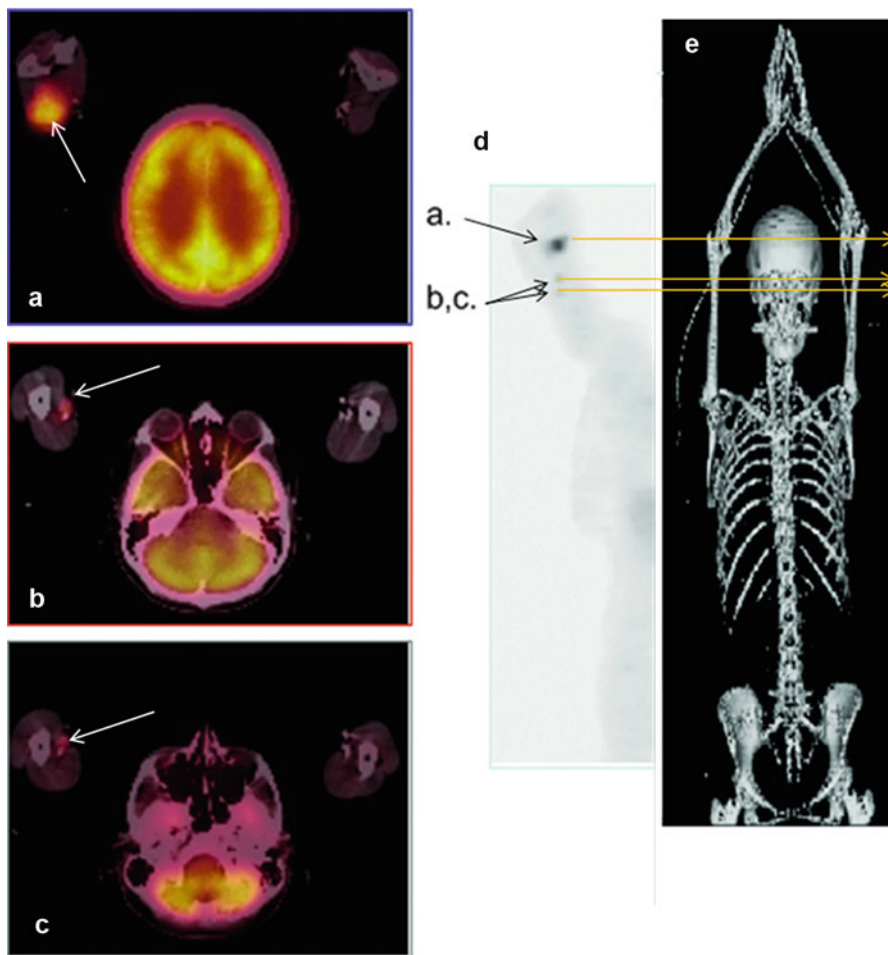
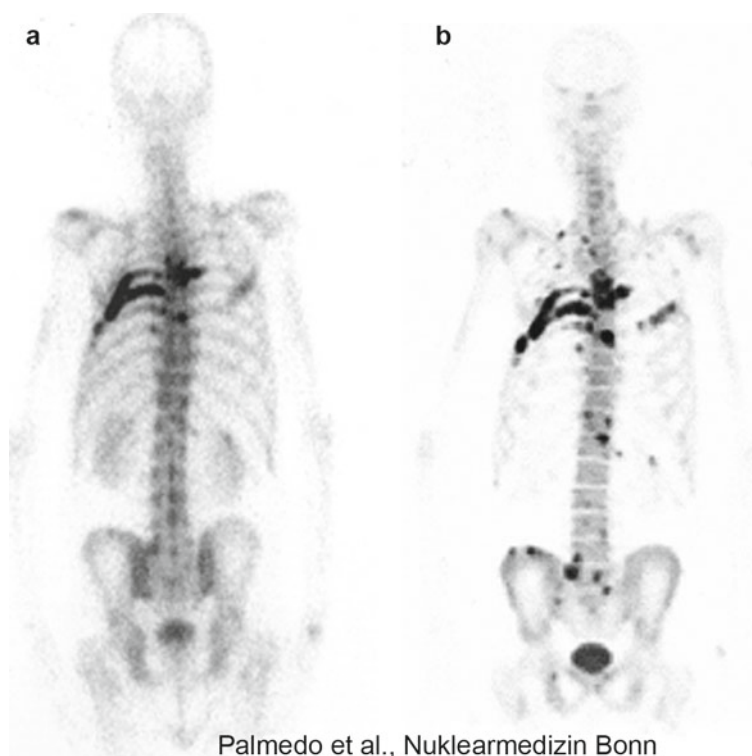


Fig. 18.3 Whole body ^{18}F -FDG-PET-CT of a patient with sarcoma of the right upper limb. ^{18}F -FDG-PET-CT has permitted, besides the primary focus (a, d) to detect 2 satellite metastases (b, c, d). Localization matched with CT-whole body topogram (e)

18.6 Labeled Amino Acids and Other RPs

^{18}F -FDG currently remains the main RP, although its main disadvantage manifests itself in the presence of a concomitant inflammation in the region under examination, which can be often observed in tumors (both in primary diagnosis and after selective local treatment). Therefore, the search for a more-specific tumor-seeking RP for these kinds of tumors is crucial. The first evaluations of using ^{11}C -thymidine and ^{18}F -thymidine, ^{18}F -tyrosine (^{18}F -FLT) give hope.

Some limited research has shown that ^{18}F -FLT PET-CT permitted discovery of signs of a tumorous lesion in all the patients with soft tissue tumors and revealed a correlation between proliferative activity and ^{18}F -FLT uptake.



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Fig. 18.4 Routine SPECT-osteoscintigraphy (a) and Na¹⁸F-Fluorid (b) In Na¹⁸F-Fluorid-PET examination (as compared with SPECT) in 76% cases additional RP pathological uptake foci have been detected, labeling neoplasms

So, for the time being there is no unequivocal evaluation of the efficiency of using ¹⁸F-FDG PET in primary tumors of the locomotive system, due to an utterly heterogeneous picture observed in this pathology. However, we should confess that the existing data are relative to the time of using mono-PET. Combined methodology will certainly improve the results and increase the informative value of examinations, especially when using CT data for correction, as well as in automatic mapping with help of modern computer programs of SPECT, CT, MRI and PET data registration. Data fusion may help make primary diagnosis and determine the dissemination of the disease as well as to characterize the morphobiological properties of the primary tumor and its deposits.

The sensitivity of whole-body Na¹⁸F-Fluorid PET-CT is higher than that of osteoscintigraphy with labeled phosphates (Fig. 18.4).

Differential diagnosis of cicatrice/living tumor tissue is possible in the future with the help of ¹¹C-thymidine (¹⁸F-thymidine) and ¹⁸F-FLT. Using ¹⁸F-FLT permits determination of the early response of tumor cells to chemotherapy. This information is necessary because it is only in such cases that it is suitable to carry out organ-preserving operations after non-adjuvant therapy.

After metal osteosynthesis operations only ^{18}F -FDG-PET is the method of choice. Semi-qualitative evaluation of PET results, especially during and immediately after the treatment (assessing the ratio tumor/unchanged tissue or SUV) will make possible an early differentiation between malignant and benign neoplasms as well as early prognosis of treatment results and of further clinical course.

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19.1 Clinical-Morphological Characteristics of Focal Brain Lesions

Central nervous system (CNS) tumors account for 4–5% of all oncological diseases and occur equally frequently in men and in women. These neoplasms are the third most common cause of death in the adult population. In Russia, every year four to seven cases of primary brain tumors are reported per 100,000 of the population, out of which 70% of patients die, and severe disability is observed among survivors in 30–40% of cases. In spite of improving surgical and conservative treatment methods, a reduction in the number of primary tumors is still not observed and the frequency of metastatic brain lesion cases is growing. So, over the last three decades the number of primary tumor cases has grown on average by 1.5 times, while the frequency of metastatic lesions has increased sixfold (Roelcke and Leenders 2001). Such an abrupt increase in frequency of metastatic brain lesions is due to their growing detectability owing to medical visualization methods; it is also connected with the tendency of growing survival rate among patients with extra-brain tumor localization, which simultaneously leads to more frequent brain metastases.

Classification of brain tumors is based on the topographic-anatomic and pathomorphological principles. The former determines the localization of the neoplasm and is important to understand the clinical picture, including the character of neurologic lesion. According to this principle, tumors are divided into supratentorial and subtentorial types and they are also distinguished depending on lateralization and relations to intra-cerebral structures. The latter principle reflects the degree of tumor differentiation, tumor growth characteristics, its tendency to malignization and metastases; it is necessary in making the prognosis of the disease and in choosing adequate treating. There are a lot of classifications of brain and spinal tumor, but the International Classification of Tumors of the CNS adopted in Lyon in 2000 has become the most widespread.

19.2 Histological Classification of Tumors of the CNS

1. Tumors out of neuroepithelial tissues
 - 1.1. Astrocytic tumors
 - 1.1.1. Astrocytoma: fibrillary, protoplasmatic, large-cell astrocytoma
 - 1.1.2. Anaplastic (malignant) astrocytoma
 - 1.1.3. Glioblastoma: giant-cell glioblastoma,
 - 1.1.3.1. Gliosarcoma
 - 1.1.4. Pilocytic astrocytoma
 - 1.1.5. Pleomorphic xanthoastrocytoma
 - 1.1.6. Subependymal giant-cell astrocytoma (tuberous sclerosis)
 - 1.2. Oligodendroglial tumors
 - 1.2.1. Oligodendroglioma
 - 1.2.2. Anaplastic (malignant) oligodendroglioma
 - 1.3. Ependymal tumors
 - 1.3.1. Ependimoma (papillary and clear cell ependimoma)
 - 1.3.2. Anaplastic (malignant) ependimoma
 - 1.3.3. Mixopapillary ependimoma
 - 1.3.4. Subependimoma
 - 1.4. Mixed gliomas
 - 1.4.1. Oligoastrocytoma
 - 1.4.2. Anaplastic (malignant) oligoastrocytoma
 - 1.4.3. Others
 - 1.5. Vascular plexus tumors
 - 1.5.1. Vascular plexus papilloma
 - 1.5.2. Vascular plexus carcinoma
 - 1.6. Gliomatosis cerebri
 - 1.7. Neuronal and mixed neuron-glial tumors
 - 1.7.1. Gangliocytoma
 - 1.7.2. Ganglioglioma
 - 1.7.3. Anaplastic (malignant) ganglioma
 - 1.7.4. Disembryoplastic neuroepithelial tumor
 - 1.7.5. Central neurocytoma
 - 1.7.6. Paraganglioma
 - 1.7.7. Olfactory neuroblastoma (esthesioneuroblastoma)
 - 1.7.7.1. Olfactory neuroepithelioma
 - 1.8. Parenchymatous tumors of the pineal body
 - 1.8.1. Pineocytoma
 - 1.8.2. Pineoblastoma
 - 1.9. Embryonal tumors
 - 1.9.1. Medulloepithelioma
 - 1.9.2. Neuroblastoma
 - 1.9.3. Ependymblastoma
 - 1.9.4. Primitive neuroectodermal tumors
 - 1.9.4.1. Medulloblastoma: desmoplastic medulloblastoma, medulloblastoma, melanin-containing medulloblastoma

2. Tumors of cranial and spinal nerves
 - 2.1. Neurinoma
 - 2.2. Neurofibroma
 - 2.3. Malignant neurinoma
3. Tumors of meninges
 - 3.1. Tumors of meningotheial cells
 - 3.1.1. Meningoma: meningotheial, fibroblastic, transitional (mixed), psammomatous, angiomatous, secretory, clear cell meningomas
 - 3.1.2. Atypical meningoma
 - 3.1.3. Anaplastic (malignant) meningoma
 - 3.2. Mesenchymal, non-meningotheial tumors
- Benign:
 - 3.2.1. Osteochondral tumors
 - 3.2.2. Lipoma
 - 3.2.3. Fibrous histiocyoma
- Malignant:
 - 3.2.5. Hemangiopericytoma
 - 3.2.6. Chondrosarcoma
 - 3.2.7. Malignant fibrous histiocyoma
 - 3.2.8. Rabdomyosarcoma
 - 3.2.9. Meningeal sarcomatosis
- 3.3. Primary melanocytic lesions
 - 3.3.1. Malignant melanoma
- 3.4. Tumors of unclear origin
 - 3.4.1. Hemangioblastoma
4. Lymphomas and tumors of blood-making tissue
 - 4.1. Malignant lymphoma
 - 4.2. Plasmocyoma
5. Tumors of germ cells
 - 5.1. Germinoma
 - 5.2. Embryonal carcinoma
 - 5.3. Endodermal sinus (yolk sac) tumor
 - 5.4. Chorioncarcinoma
 - 5.5. Teratoma
6. Cysts and tumor-like lesions
 - 6.1. Rathke's pouch cyst
 - 6.2. Epidermoid cyst
 - 6.3. Dermoid cyst
 - 6.4. Colloid cyst of the III ventricle
 - 6.5. Entherogenic cyst
 - 6.6. Neuroglial cyst
 - 6.7. Granular cell tumor (choristoma, pituicytoma)
 - 6.8. Neuronal hamartoma of hypothalamus
7. Tumors of the region of the Turkish saddle
 - 7.1. Hypophyseal adenoma

- 7.2. Hypophysis cancer
- 7.3. Craniofaringioma
- 8. Tumors ingrown into cranial cavity
 - 8.1. Paranglioma (chemodectoma)
 - 8.2. Chordoma
 - 8.3. Chondroma
 - 8.4. Chondrosarcoma
 - 8.5. Cancer
- 9. Metastatic tumors
- 10. Unclassifiable tumors

Gliomas and meningiomas make up more than 65–70% of all primary brain neoplasms, another 15–20% are neurinomas and hypophyseal adenomas, and only some 10–15% fall in the remaining large group of tumors (Ribom et al. 2001). Among malignant neoplasms, gliomas (77%) and metastases from extra-brain tumors prevail.

Prognosis in anaplastic astrocytomas (AA) and glioblastomas (GB) is unfavorable. In spite of active tactics of neurosurgeons and radiologists relative to these tumors, the life span of GB patients does not exceed 2–3 years (Baba et al. 1997; Castillo 1998). The development of the tumor process depends on the degree of malignancy (aggressiveness), growth rate and tumor localization. For example, in glioblastoma gross decompensation of the tumor process may be observed within several months and even days, while omitting other phases. At the same time, slow-growing benign meningiomas and astrocytomas may remain for years in the phase of clinical compensation or subcompensation.

The dissemination of malignant gliomas is possible by way of invasion or metastasizing. These tumors are able to extend to adjacent brain lobes and even to the hemispheres. At the same time, meningiomas are usually well delimited from the medullary substance and are characterized by slow expansion growth. Changes in brain tissues are due to the expansion of the neoplasm with consequent compression of tissue, as well as to the damaging effect of toxic factors related to the vital activity of tumor cells, and resulting in the development of oedema and necrosis of adjacent brain tissues (Martinez-Mata et al. 1999; Otte 1999). Among the earliest clinical manifestations of brain tumors, convulsive seizures, paresthesias, headaches, (rarer) central vomiting, vertigos, pareses and paralyses prevail.

Tumor process in the skull base may be accompanied by atrophic changes of optic nerves, and appearance of congested papilla in the eye ground.

Tumors of the glial family have in common their origin from astrocytic tissue, presence of more or less apparent glial-fibrous component, the infiltrative character of growth and tendency to metastases and relapses. It should be noted that in the absence of treatment more than 10% of benign astrocytomas malignize. At the same time, after non-radical surgical intervention or conservative treatment more than 50% of neoplasms transform (Piepmeier 1987).

Meningiomas grow out of meninx cells and usually adjoin bone structures of the skull (Black 1993), quite often infiltrating them (Ringel et al. 2007). Meningiomas most often localize in the region of the parietal, frontal and temporal bones of the

skull, parasagittally, in the region of the falx cerebris and sinuses (falx meningiomas). Basal meningiomas most often proceed from the wings of the sphenoid bone, tubercle of the Turkish saddle, olfactory fossa and parasellar structures. A distinction of basal meningioma is lesion cerebral nerves and the vessels of the brain base. It is due to the involvement in the tumor process of adjacent structures, nerves and vessels (Friedlander et al. 1999). Meningiomas of the posterior skull fossa more often grow from petrosal bones. In these cases they have to be differentiated from neurinomas of acoustic nerve and cholesteatomas (Krayevskiy et al. 1982). The structure of meningiomas may be lobulous or solid. Benign meningiomas more often have a homogeneous structure, while malignant ones are characterized by the presence of calcification, hemorrhages, necroses, cysts (Yamada et al. 1996). In malignant meningiomas, peritumorous oedema may be also present. They are distinguished by their expansive growth and apparent mass effect (Stafford et al. 1998; Mantle et al. 1999).

The differentiation of tumors by degree of malignancy is crucial both for disease prognosis and for the choice of therapeutical management. For example, with tumors of degrees III–IV life span is in most cases only 9–10 months. With tumors of degrees I–II, the 5-year survival rate reaches 50–75% (Kleihues et al. 1993; Groos et al. 1998).

It should be noted that the clinical signs of tumors are not pathognomonic and can be observed in many diseases. The clinical manifestations of tumors in most cases are related to their localization and effect on adjacent brain structures, which often enables determination of their location; however, the moment of the appearance of pathological symptoms and their intensity may range within quite wide limits. The diversity of pathologic processes underlying CNS masses as well as the similarity of neurologic symptoms restrains the possibilities of their clinical differential diagnosis.

19.3 Methods of Radiodiagnosis of Brain Tumors

Under contemporary conditions the diagnosis of volumetric brain formations is provided by a complex examination consisting of clinical-biological and instrumental methods (Konovalov et al. 1997). During such an examination, the following main tasks are to be solved: the identification of the pathologic process (nosologic diagnosis), spatial localization (topical diagnosis) of the formation, determination of its biological nature (histological diagnosis), detection of continued growth, assessment of response to treatment. Possible choice of a parcel of the neoplasm for puncture biopsy, monitoring of the state of benign tumors at high risk of malignization also have some significance.

In solving these problems, high-tech radiodiagnostic methods (MRI, CT, SPECT and PET) are of paramount importance (Konovalov et al. 1997; Brunelle 2000; Kornienko and Pronin 2006).

X-ray (craniography) for a long time was the only method of radiodiagnosis of brain tumor and skull lesions. However, this method permits to obtain information only on the state of bone structures and consequently to judge indirectly, on the basis of secondary changes occurring in them, the presence of brain masses. In the mid 1950s the

method of roentgen angiography appeared which permitted to solve the problem of visualization of brain vessels (Konovalov et al. 1997). The method is still successfully applied in neurooncological clinical practice, primarily in X-ray endovascular interventions. However, X-ray angiography is an invasive examination method and it does not always allow the differential diagnosis of formations and assessment of their volume and influence on adjacent brain structures.

A breakthrough in radiodiagnosis is associated with the appearance and development of CT and MRI. These methods have a high resolving capacity. They enable the detection of structural changes occurring in the brain in the presence of different pathological processes and to obtain fairly accurate information on solid brain masses [information on the location, form, dimensions and structure of brain masses (Konovalov et al. 1997)].

Compared with CT, MRI has a number of advantages, among which count high contrast resolution, possible assessment of different tissue characteristics, and multi-projection image reconstruction, all of which make MRI the method of choice in neurooncology. MRI permits to assess structures situated near the base of the skull, which are not well visualized by CT due to frequent presence of artifacts. Absence of radiation exposure renders this method particularly valuable for pediatrics. CT is a relatively cheap and available method and is used primarily in urgent diagnosis in order to exclude brain formations. CT is the only method permitting the detection of calcium deposits inside the tumor, which may be important for differential diagnosis. CT is not efficient in presence of isodense formations.

CT and MRI in neurooncology have proved to be most efficient with use of contrast effect (Kornienko and Pronin 2006; Sergeev et al. 2007). Admittedly, it should be confessed that in spite of much progress in diagnosis and differential diagnosis of brain tumors due to the introduction of CT and MRI into clinical practice, many functional matters are still outside the range of these methods of diagnosis. This concerns first of all the biological characteristics of tumors, such as the state of metabolism, degree of malignancy of tumor cells, their reparative capacities, vascularization, DNA synthesis rate, sensitivity to hypoxia, etc. Using contrast in MRI helps to determine precisely the structure, volume and localization of formations, and their relations to surrounding tissues, as well as the state of the blood–brain barrier. However, the experience of using contrast MRI has shown that the level of accumulation of contrast agent depends on the state of microcirculation, degree of change in permeability of the blood–brain barrier, volume of intercellular space in the formation under evaluation and that it does not always permit assessment of the nature of lesion (Sergeev et al. 2007). Differentiating radiation necrosis from continued growth of tumors is not possible. For example, presence of changed or damaged tissues in the post-operation region under examination by means of contrast MRI may give rise to false-positive diagnosis of tumors due to injuries to the blood–brain barrier occurring in this case (Hagge et al. 2001). The specificity of MRI with contrast enhancement in the diagnosis of glioma relapses does not exceed 70% (Yamada et al. 1999).

CT or MRI evaluation of the response of neoplasms to treatment is based, as a rule, on detecting changes in dimensions and structure of formations. However, these changes, in case of successful treatment, are reflected in scans only after a

several-month lapse. Therefore, the early-term evaluation of treatment efficiency is difficult. Besides, a change in dimensions of pathologic formations or in their anatomic structure cannot always serve as a reliable criterion for the biological state of tumor cells and for the efficiency of treatment. The most objective information for these purposes can be obtained by means of methods of radionuclide diagnosis.

Methods of radionuclide visualization were described by G. Moor in 1948 and started to be used in differential diagnosis of volumetric brain formations in late 1960s. Using radionuclide diagnosis in neurooncology is based on the possibility of visualizing malignant brain neoplasms with some radiopharmaceuticals (RPs). Nowadays technologies of nuclear medicine (SPECT and PET) have received the widest use among all methods of radionuclide diagnosis (Steinling 1997, Hustinx and Alavi 1999, Schwarz and Kuwert 2000).

Single photon emission computer tomography (SPECT) was developed in late sixties. The method is still developing systematically and is currently widely used in clinical practice. It should be noted that progress in the development of radionuclide diagnostic methods is associated not only with developing and improving radiodiagnostic apparatuses but also with the appearance of new diagnostic media and RPs. The following RPs are most widely used when using SPECT in neurooncology: $^{201}\text{TlCl}$, $^{99\text{m}}\text{Tc}$ -techneteryl ($^{99\text{m}}\text{Tc}$ -MIBI), $^{99\text{m}}\text{Tc}$ -pyrphotech-erythrocytes, 1–3- ^{123}I -methyltyrosine (Plotkin et al. 2005) and others. These RPs are non-specific tumor markers. They are actively accumulated in malignant neoplasms and so permit their visualization. However, simultaneous uptake of these RPs in aponeurosis, lymphoid tissue and in the hypervascular regions of the head and neck is observed (Bader et al. 1998, 1999). This decreases their diagnostic value and makes them poorly informative in the differential diagnosis of patients with brain tumors. The amino acid tyrosine 1–3- ^{123}I -methyltyrosine (^{123}I -IMT) is a tumor marker; the mechanism of its accumulation in brain tumors is identical with that of methionine uptake (Langen et al. 2006). ^{123}I -IMT SPECT is used for determining tumor dimensions and for diagnosis of relapses (Plotkin et al. 2004, 2005). ^{111}In -Octreotide, a marker of somatostatin receptors, is used for diagnosis of meningioma relapses. At the same time, the capacities of neoplasm diagnosis with help of these RPs are limited due to a relatively low resolving capacity of SPECT, which makes particularly difficult their use for radiotherapy planning and for planning of neurosurgical operations.

Further progress in diagnosis, and particularly in the differential diagnosis of volumetric brain formations, is associated with the development and introduction into clinical practice of PET in the late 1970s. PET differs from SPECT in its higher resolving capacity and sensitivity, possible use of attenuation correction, and possible obtention of tomographic images in the dynamic regime. As RPs for PET, biologically active substances labeled with cyclotron-generated ultra-short-lived radionuclides (USLRs) are used. ^{18}F -fluorodeoxyglucose (^{18}F -FDG) has become the first RP for PET. Early research has shown that uptake of ^{18}F -FDG correlates to the degree of malignancy of brain tumors and has a certain prognostic value (Hagge et al. 2001). It has been found out that ^{18}F -FDG PET makes it possible to assess the degree of malignancy of tumors (Herholz et al. 1993; De Witte

et al. 2000) and to choose optimum sites for biopsy (Levivier et al. 1995). The method is actively used for differentiating brain lymphomas and toxoplasmosis foci in patients with immune deficiency syndrome since FDG is not accumulated in lesion foci in toxoplasmosis (Villringer et al. 1995). It has been suggested using ^{18}F -FDG for detecting malignization of benign tumors (De Witte et al. 1996) and for differential diagnosis of the continued growth of malignant gliomas and radiation necrosis (Glantz et al. 1991). Presently, these early suggestions are being put in doubt (Wong et al. 2002; Spence et al. 2003). For example, due to high uneven glucose accumulation in the cortex, it is difficult to determine the boundaries of the tumor and in many cases the tumor itself. Besides that, benign astrocytomas are not visualized in ^{18}F -FDG PET because of low metabolism in them. For the same reason, ^{18}F -FDG PET has low sensitivity in detecting brain metastases (Larcos and Maisey 1996).

Compared with ^{18}F -FDG, labeled amino acids such as ^{11}C -methionine (^{11}C -MET) (Benard et al. 2003; Ogawa et al. 1996) and ^{18}F -fluoroethyltyrosine (^{18}F -FET) (Wester et al. 1999) have a number of advantages in diagnosing brain tumors, especially benign astrocytomas and brain metastases. Owing to low accumulation of amino acids in brain tissue, these RPs permit to differentiate tumors from non-tumor diseases (Floeth et al. 2006), to precisely define tumor boundaries, its continued growth and relapses (Popperl et al. 2004; Pauleit et al. 2005), and to determine a representative part of the tumor for biopsy planning (Wieder et al. 2003; Sadeghi et al. 2007; Stockhammer et al. 2008). Besides ^{18}F -FDG and labeled amino acids, other RPs are used for diagnosis of brain tumors. For example, PET with the marker of somatostatin receptors ^{68}Ga -DOTA-D-Phe1-Tyr3-octreotide (^{68}Ga -DOTATOC) is successfully used in diagnosis of meningiomas (Henze et al. 2001). PET with ^{18}F -choline, the indicator of membrane-forming speed, permits to visualize many brain tumors and can be used for detecting brain metastases of prostate cancer. It has been suggested using ^{15}O -water for assessing the degree of vascularization of brain tumor formations (Medvedev et al. 1996; Skvortsova et al. 2001a; Lüdemann et al. 2008). The hypoxia marker ^{18}F -FMISO is of interest for planning and efficiency assessment of brain tumor radiotherapy (Cher et al. 2006). At the same time, using PET with the DNA synthesis marker ^{18}F -fluorothymidine (^{18}F -FLT), suggested for brain tumor diagnosis, proves to be inefficient due to apparent dependence of ^{18}F -FLT uptake on the impairment of the blood-brain barrier (Saga et al. 2006).

It should be noted that high cost of automated modules and RP production on the whole imposes some constraints on their choice and production, and compels to choose the most informative of them. Of some importance is the possibility of quantitative evaluation of PET data with the help of multicompartment mathematical models developed for many RPs (Roelcke and Leenders 2001).

The improvement of the software for retrospective fusion of different modality images has marked an important stage of development and introduction of PET (Pietrzyk et al. 1994). It is known that localization of pathologic finds is often made difficult by absence of articulate anatomic reference points in the PET scans. That is why the fusion of PET and MRI or CT data is an important precondition for their

correct topographic-anatomic interpretation (Paulus and Peiffer 1989). Recently an apparatus combining the capabilities of PET and CT, the so-called PET-CT, has been created (Beyer et al. 2001; Beyer and Townsend 2002). It enables to mark out the boundaries of formations and to assess their biological properties which are important for primary diagnosis of tumors and for diagnostic decision making. It should be noted that development of methods of fusing multimodal images such as PET-CT has accelerated the integration of PET into the process of radiotherapy and stereotactic biopsy planning. However, in neurooncology PET-CT does not have as significant advantages over PET alone as it does in diagnosing extra-cranial tumors, because retrospective fusion of MRI and PET scans is possible. PET-MRI, providing a combination of the advantages of PET and MRI in a single examination, seems to be more promising for the diagnosis of brain diseases. Prototypes of such scanners are being clinically tested (Seemann 2005).

On the basis of the world scientific literature, we can state that PET is universally admitted to be an important diagnostic tool in neurooncology as a promising functional method of radiodiagnosis and differential diagnosis of tumors. This is due to the technical capabilities of PET and the properties of RPs.

19.4 PET RPs Used in Neurooncology

19.4.1 ^{18}F -FDG PET

In 1982, Di Charo and coworkers first pointed out the possibility of using ^{18}F -FDG PET for visualizing malignant brain tumors. High glucose uptake in malignant tumors is conditioned by high expression of the transporter GLUT1 and by hyperactivity of hexokinase. It has been established that the degree of blood-brain barrier injury and of vascularization of brain tumors do not have an impact on ^{18}F -FDG uptake (Di Chiro 1987; Padma et al. 2003). Subsequently there appeared reports of using ^{18}F -FDG for the differential diagnosis of neoplasms, detection of continued growth, treatment efficiency evaluation and disease prognosis in patients with different tumors (De Witte et al. 2000).

At the same time, it should be admitted that data on the diagnostic capabilities of ^{18}F -FDG still remain conflicting (Lacic et al. 1997). Most authors consider there to be a direct correlation between the level of ^{18}F -FDG uptake and the degree of malignancy of the tumor; they think that high ^{18}F -FDG uptake is characteristic for malignant tumors (De Witte et al. 2000). Other authors are more reserved in evaluating the efficiency of using ^{18}F -FDG for differential diagnosis of malignant brain tumors; they accentuate some shortcomings of this RP, the main of which being high glucose uptake in the cortex and low ^{18}F -FDG uptake by some malignant tumors (Meyer et al. 2000, 2001). Undoubtedly, the physiological uptake and focal asymmetry of glucose metabolism provoke some difficulty in visualizing neoplasms situated in the cortex with use of ^{18}F -FDG. At the same time, fusion of PET and MRI images permits delimitation of the region of interest and precise assessment of the level of metabolism in it, which in part helps solve the problem.

Numerous studies have been devoted to the choice of criteria for differentiating malignant and benign brain tumors with use of ^{18}F -FDG (Delbeke et al. 1995, Meyer et al. 2001).

The most informative among existing data assessment methods is the one using color scale (RGB or Hot Metal) combined with measuring a semi-quantitative index, the accumulation index, which reflects the ratio of radioactivity accumulated in the tumor to the unchanged cortex.

It has been established that as the threshold value of FDG T/NT ratio grows, the sensitivity of the method decreases and its specificity increases (Kostenikov et al. 2002). When the cut-off criterion for malignant tumors is an FDG T/NT ratio ≥ 0.9 , the maximum possible specificity is reached, approaching 100%, and the sensitivity is also relatively high (82%). A limitation of this approach consists of the dependence of T/NT ratio for FDG on the level of glucose metabolism in the unaffected brain tissue. It is accounted for by glucose metabolism disturbance under the general influence of the tumor, which can be observed in cortex regions both ipsilateral and contralateral with regard to the tumor.

Cases have been described when a focus of epileptic activity in parts adjacent to the tumor or situated in the area of radiation necrosis was wrongly interpreted as an area of tumor malignization (Sasaki et al. 1996). Differences in glucose uptake (FDG T/NT ratio) between tumors of degrees I-II of malignancy and those of degrees III-IV are significant, but differentiation between tumors of degrees III and IV with use of ^{18}F -FDG is not possible (De Witte et al. 2000). In some earlier reports it was demonstrated that the level of ^{18}F -FDG uptake in the tumor is comparable in informative value with histological conclusion (De Witte et al. 1996; Derlon et al. 2000). Presently these data are being questioned. In a number of studies (De Witte et al. 2000, Padma et al. 2003) devoted to the investigation of the widest spread neoplasm group (gliomas), it has been showed that the glycolysis rate in the tumor determined according to T/NT ratio may be used as a prognostic criterion: a high level of glucose metabolism in the tumor is estimated as an unfavorable prognostic factor. However, according to research done in recent years, this rule is not universal. In particular, high accumulation of ^{18}F -FDG in oligodendrogliomas is due to characteristic chromosome injuries conditioning high sensitivity to chemotherapy, which is a favorable prognostic factor (Walker et al. 2004; Stockhammer et al. 2007).

So it follows with evidence that ^{18}F -FDG PET is a highly informative means of diagnosis of malignant brain tumors. However, many aspects of use of this RP in neurooncology are still not completely determined. Among limitations of ^{18}F -FDG PET in neurooncology, we should also rate high uptake of ^{18}F -FDG by macrophages in foci of inflammatory alterations (Jager et al. 2001). In some cases it is possible to overcome this limitation by using delayed (two-phase) scanning. The diagnosis of benign brain tumors and their differentiation from non-tumor formations are very difficult when ^{18}F -FDG is used.

The problems of identifying brain tumors, including benign ones, and of differentiating them from non-tumor diseases can be, as a rule, efficiently solved by PET with labeled amino acids (^{11}C -MET or ^{18}F -FET) (Floeth et al. 2006).

19.4.2 ^{11}C -methionine (^{11}C -MET) and Other Labeled Amino Acids

The advantage of ^{11}C -MET over ^{18}F -FDG is its high uptake in neoplasms in combination with low accumulation in the cortex, which provides visualization of tumors. It has been established that ^{11}C -MET PET enables to precisely delimit tumor boundaries, to differentiate edema from neoplasms and to detect both malignant and benign tumors (Jager et al. 2001; Chung et al. 2002; Wieder et al. 2003).

Some authors point out the high informative value of ^{11}C -MET PET in differentially diagnosing gliomas: the sensitivity of this method is 89–90% and its specificity ranges from 94% to 100% (Skvortsova et al. 2001b; Chung et al. 2002). This method is also informative for the diagnosis of brain metastases (Tsuyuguchi et al. 2003). The causes of uptake of methionine in tumors are not completely examined. It is considered that it is uptaken in high quantities due to high proliferation rate in neoplasms. It has an impact on the active RP transfer through the cell membrane of tumors (Ribom et al. 2002). Methionine is transported to a tumor cell by means of active transfer with participation of the transporters LAT-1 and LAT-2 (Jager et al. 2001).

The most important aspect of using ^{11}C -MET is evaluating the effects of benign brain tumor treatment, which is possible with its help (Nuutinen et al. 2000; Ribom et al. 2002). It has been determined that a decrease in uptake of this RP in tumors during treatment objectively reflects the positive effect of conservative therapy (Iwai et al. 2001; Muhr et al. 2001; Gudjonsson et al. 2000).

Recently ^{11}C -MET has been used to choose the target in stereotactic biopsy of neoplasms (Wieder et al. 2003; Sadeghi et al. 2007). In a number of studies it has been shown that the uptake of this RP in benign gliomas is significantly lower than in malignant ones (Skvortsova 2001). Nevertheless, the value of this approach for assessing the degree of malignancy of gliomas is put to doubt (Moulin-Romsée et al. 2007). One of shortcomings of ^{11}C -MET is its high accumulation in unchanged endocrine glands, including hypophysis. High accumulation of this RP in inflammation foci (uptake by macrophages and granulocytes) and in intracerebral hematomas in blood–brain barrier injuries has been described, which makes the differential diagnosis of tumor diseases difficult and may give rise to false-positive conclusions (Hanakawa et al. 1998).

The indicated limitations of ^{11}C -MET have stimulated the intensive development of other RPs, such as ^{11}C -thymidine (Jager et al. 2001), labeled amino acids including ^{11}C -tyrosine, fluoroboronophenylalanine (Imahori et al. 1998), ^{18}F -fluoroethyl-tyrosine (^{18}F -FET) (Weber et al. 2000) and a number of others. ^{18}F -FET is considered to be the most promising among the above mentioned RP. Due to a longer half-life period of ^{18}F (compared with ^{11}C) this RP can be transported, like ^{18}F -FDG, which, together with simple methodology of synthesis and possibility to examine up to ten patients daily, expands the possibilities of its clinical use.

Unlike ^{11}C -MET, ^{18}F -FET is not accumulated in macrophages and granulocytes and therefore has a higher specificity (Stöber et al. 2006). Transport to tumor cells is not connected with crossing the blood–brain barrier and is realized by means of active transfer with help of the transporter LAT-2. Accumulation of ^{18}F -FET in tumors depends on the degree of angiogenesis and density of tumor cells

(Stockhammer et al. 2008). Unlike ^{11}C -MET, ^{18}F -FET does not participate in protein synthesis and is a marker of amino acid transport (Langen et al. 2006).

Some authors point out the possibility of determining the degree of malignancy of gliomas by reference to ^{18}F -FET accumulation rate in tumor. This method is based on a lower ^{18}F -FET uptake by benign gliomas compared with malignant ones (Pöpperl et al. 2006a).

Besides labeled glucose and amino acids, the diagnostic capabilities of other labeled biologically active natural substances have been studied, such as acetate, choline, fatty acids, putrescine, deprenyl, fluoro-dihydroxyphenylalanine (DOPA). It has been showed that ^{11}C -acetate is better accumulated in tumors then labeled aromatic (synthetic) fatty acids, for example ^{11}C -phenylacetate and ^{18}F -fluorophenylacetate (Jonson and Welch 2002). ^{11}C -Choline, being part of cell membranes, also permits the visualization of malignant gliomas and to differentiate them from benign brain tumors and non-tumor formations. ^{11}C -Putrescine and ^{11}C -deprenyl showed high uptake in tumors (De Reuck et al. 1999). Relatively recently, ^{18}F -DOPA has been described as a marker of brain tumors. In our studies we have shown that the labeled fatty acid ^{11}C -sodium butyrate (^{11}C -SB) is accumulated in high amounts in malignant and some hypervascular benign tumors. ^{11}C -SB permits to simultaneously assess some parameters characterizing properties of neoplasms, such as vascularization, the rate of uptake and utilization of fatty acids, and the speed of metabolic processes (Kostenikov et al. 2002).

19.5 Methodological Aspects of Using PET in Brain Tumors

19.5.1 PET Scanning

The characteristics of PET emission scanning methods for some RPs widely used in neurooncology are summarized in Table 19.1

Emission scanning is preceded by 10-min transmission scanning with calibration sources of ionizing radiation (^{68}Ge) for attenuation correction. The effective dose for 10 min is 0.07 mSv. When PET-CT scanners are used, transmission scanning is provided by CT; the effective dose in CT is from 1.2 to 3 mSv.

From 20–30 min before to 15–20 min after the introduction of ^{18}F -FDG the patient is sound and light insulated in order to exclude the physiological uptake of the RP in the cortex. ^{18}F -FDG is introduced in the form of a jet intravenous injection in the volume of 1.5 mL 35–40 min before the beginning of the emission static scanning into a peripheric vein of the limbs. The diagnostic dose of ^{18}F -FDG in brain examination makes up 100 MBq/m² per body surface (150–250 MBq/m² for an examination). The coefficient for calculation of the effective dose when introducing ^{18}F -FDG is 0.019 mSv/MBq. When introducing the diagnostic dose of RP, the effective dose is from 2.85 to 4.75 mSv for an examination.

Static brain scanning lasts 20 min and is done in 2D or 3D regimes with use of the matrix 128×128 and with image enlargement by 1.5 times. If quantitative analysis is necessary, dynamic scanning is implemented. Dynamic scanning with ^{18}F -FDG is

Table 19.1 The characteristics of the methods of PET scanning

RP	The measured index	Diagnostic RP dose (MBq/m ²)	Factor for calculating the effective dose in adults (mSv/MBq)	Onset of scanning (min)	Scan duration (min)	Scan regime
¹⁸ F-FDG	Glucose metabolism (transmembrane transport) rate	100	19.0×10^{-3}	35–40 0	20 55	Static Dynamic
¹¹ C-MET	Protein synthesis rate	350	2.0×10^{-3}	5 0	20 20	Static Dynamic
¹⁸ F-FET	Amino acid transport rate	150	16.5×10^{-3}	10 0	20 40	Static Dynamic
⁶⁸ Ga-DOTATOC	Somatostatin receptor level	50	27.4×10^{-3}	60	20	Static
¹¹ C-sodium butyrate	Fatty acid metabolism	350	3.5×10^{-3}	0	30	Dynamic
¹⁵ O-water	Regional blood flow rate	500	0.93×10^{-3}	0	1	Static

done under the same conditions as static scanning. It starts immediately after RP introduction and lasts 50 more minutes.

Brain scanning with ¹¹C-MET lasts 10–20 min and is done in the same regime as that with ¹⁸F-FDG, 5 min after the jet-mediated intravenous introduction of 350 MBq/m² of RP. As a rule, 370–950 MBq of RP is used for one PET examination. The coefficient for calculation of the effective dose when introducing ¹¹C-MET is 0.0074 mSv/MBq. When introducing the diagnostic dose of RP its effective dose is from 2.74 to 7.0 mSv for an examination. When a PET-CT scanner with lutetium oxyorthosilicate (LSO) or gadolinium oxyorthosilicate (GSO) crystals is used, the diagnostic dose of ¹¹C-MET is lower than the one for PET scanner and is 250–700 MBq.

A brain scan with ¹⁸F-FET may be done in the same static or dynamic regimes as that with ¹⁸F-FDG. Patients are administered a protein-free diet 12 h before the examination. A 20-min static scanning is implemented 10 min after the jet-mediated intravenous introduction of 150 MBq/m² of ¹⁸F-FET. As a rule, 250–300 MBq of RP are used for one examination. Dynamic scanning begins immediately after RP is introduced and lasts for 40 min. The coefficient for calculating the effective dose when introducing ¹⁸F-FET is 0.0165 mSv/MBq. When introducing the diagnostic dose of the RP the effective dose is from 4.13 to 4.95 mSv for an examination. When a PET-CT scanner with LSO or GSO crystals is used the diagnostic dose of ¹⁸F-FET is lower than that for PET and amounts to 185–200 MBq. Immediately before the emission scan, a diagnostic scan with contrast enhancement is recommended.

A 20-min PET-CT brain scanning with ^{68}Ga -DOTATOC is done in the static regime 60 min after the jet-mediated intravenous introduction of 50 MBq/m² of RP. Normally 70–120 MBq of RP is used for one examination. The coefficient for calculation of the effective dose when introducing ^{68}Ga -DOTATOC is 0.0274 mSv/MBq. When introducing the diagnostic dose of the RP the effective dose is from 1.92 to 3.29 mSv for an examination.

A 31-min scanning with ^{11}C -SB is done in the same regime as that with ^{18}F -FDG, immediately after the jet-mediated intravenous introduction of 350 MBq/m² of RP. Usually 550–750 MBq of RP are used for one examination. The coefficient for calculation of the effective dose when introducing ^{11}C -SB is 0.0035 mSv/MBq. When introducing the diagnostic dose of the RP the effective dose is from 1.9 to 2.6 mSv for an examination.

The reconstruction of sonograms for PET is done by way of back projection reconstruction with the use of a Hanning-filter and 2- to 5-times zoom of the image. As for PET-CT, the interactive filter of reconstruction with similar enlargement is normally used.

19.5.2 Analysis of PET Images

In order to eliminate symmetry irregularities of positioning, the primary ^{18}F -FDG PET image may be rotated sequentially in three projections, satisfying the following demands:

- Interlobar fissure in the transaxial sections should be parallel to the vertical axis of the screen
- Basal temporal lobes in the coronary cuts are parallel to the horizontal axis of the screen
- Poles of the frontal and occipital lobes in the middle sagittal section are parallel to the horizontal axis of the screen

From 15 to 28 transaxial sections, 5-mm thick, are kept (depending on the resolving capacity of the tomography), containing the whole brain image so that the first section represents convex cortices, and the last one represents basal parts including the cerebellum. (Fig. 19.1). Such a standardization of tomoscintigrams allows using the stereotactic anatomic brain atlas to verify anatomic structures of the brain and to localize masses. However, for the purpose of quantitative analysis it is preferable to use more accurate axial sections, for which reason patient positioning demands a special preparation.

We should mention the following characteristics of the normal distribution of the indicated RPs.

In ^{18}F -FDG PET the level of cortical accumulation is high, the RP distribution is focally inhomogeneous, and asymmetry may reach 20% (Fig. 19.1).

In ^{11}C -MET PET the level of accumulation in the cortex is low; the RP distribution is homogeneous. In the basal sections the hypophysis, lacrimal, salivary and parotid glands as well as the tonsils of the nasopharynx are visualized (Fig. 19.2a).

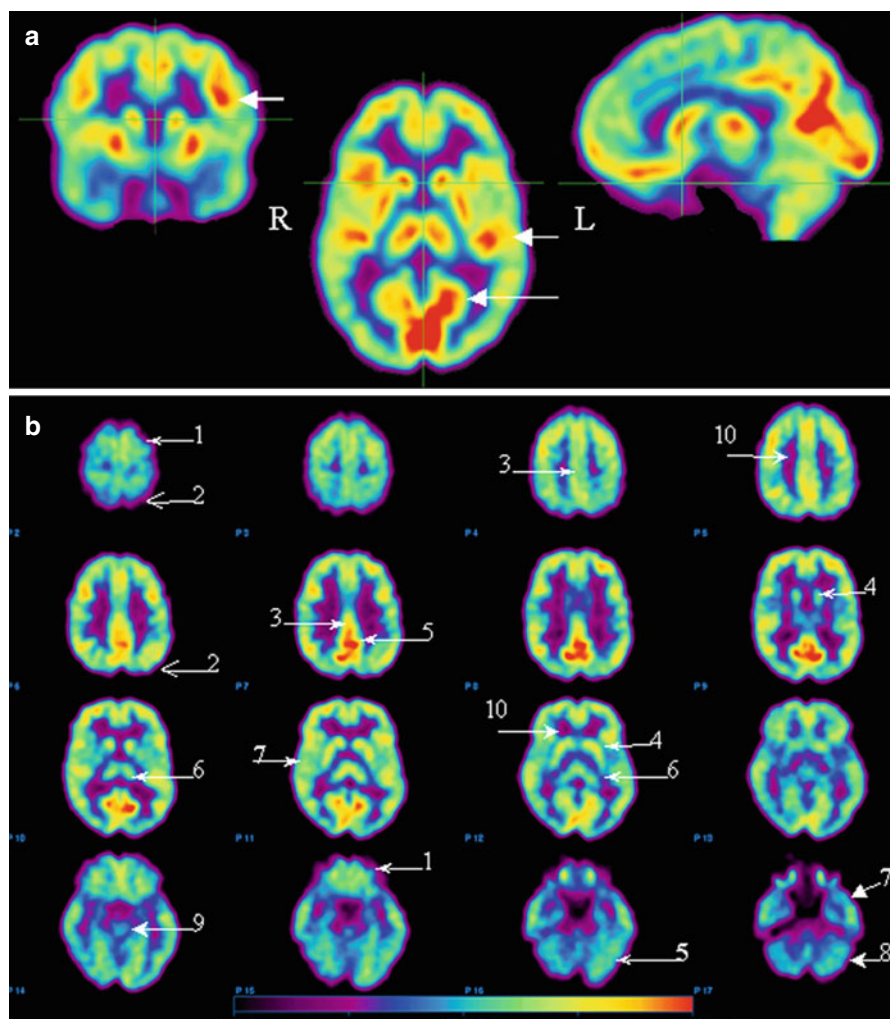


Fig. 19.1 ^{18}F -FDG PET: Normal ^{18}F -FDG distribution in the cerebral cortex. (a) Standard positioning for brain examination. Three projections demonstrate all the cortical segments. Asymmetric physiologic foci of RP uptake are indicated with arrows. (b) Axial sections of the brain from convexital to basal segments: 1 – frontal lobe, 2 – parietal lobe, 3 – cingulated gyrus, 4 – head of caudate nucleus, 5 – occipital lobe, 6 – thalamus, 7 – temporal lobe, 8 – cerebellum, 9 – truncus cerebri, 10 – white matter

In ^{18}F -FET PET the level of accumulation in the cortex is low; the distribution of the RP is homogeneous. Basal ganglia have a higher uptake of amino acids. Besides, high accumulation of ^{18}F -FET is observed in the endothelium of venous sinuses and in the aponeurosis, which can be used in fusing PET and MRI images (Fig. 19.2b).

^{68}Ga -DOTATOC does not cross the unchanged blood–brain barrier, consequently its accumulation in the cortex is low. RP uptake is observed in the hypophysis and

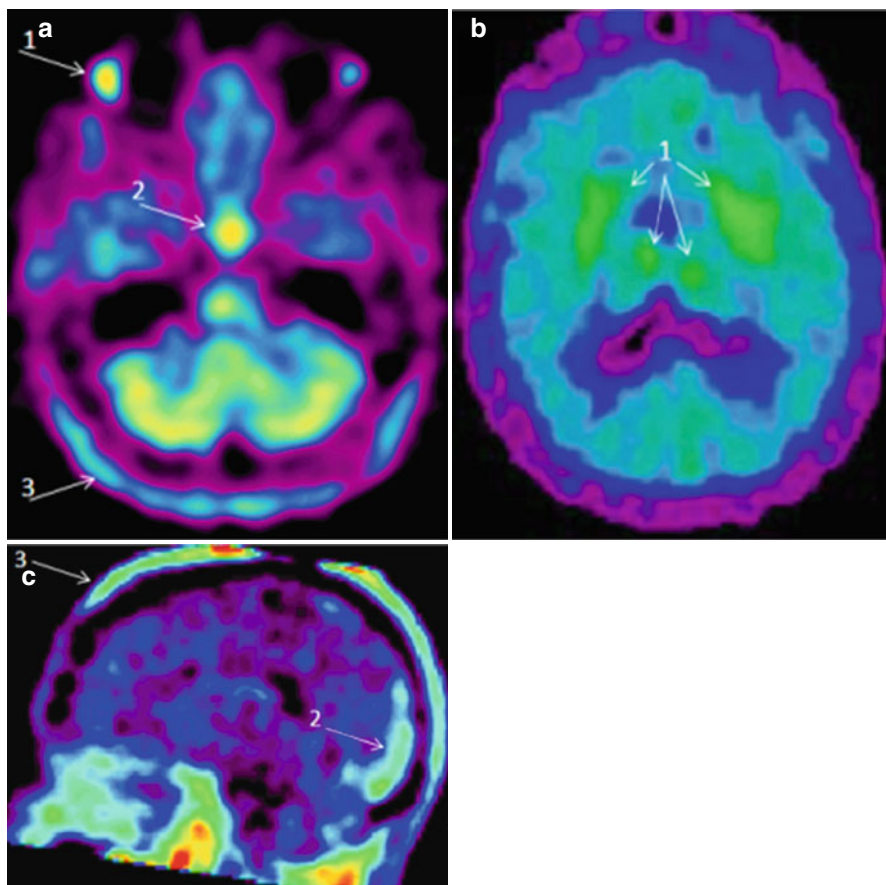


Fig. 19.2 Normal distribution of labeled amino acids in the brain. (a) In ^{11}C -MET PET amino acid uptake is observed in the tear glands (1), hypophysis (2) and aponeurosis (3). (b, c) In ^{18}F -FET PET uptake is observed in the basal ganglia (1), endothelium of venous sinuses (2) and aponeurosis (3)

aponeurosis. The hypophysis has a high level of somatostatin receptors and accumulates ^{68}Ga -DOTATOC in high amounts, which can cause certain problems in detecting meningiomas of the Turkish saddle (Fig. 19.3).

In ^{11}C -SB PET the level of cortical accumulation is low; the RP distribution is homogeneous. In the basal sections the hypophysis, lacrimal, salivary and parotid glands as well as the tonsils of the nasopharynx and muscles are visualized (Fig. 19.4). For visual analysis, the summed accumulated images of the vascular phase (from the 1st to 6th frames) and tissular phase (from the 7th to 31st frames) are used.

PET scans are visualized visually and quantitatively. T/NT ratios (most active part of tumor/cortex) are used as quantitative cutoff criteria to exclude malignant tumors. A T/NT ratio ≥ 0.9 in ^{18}F -FDG PET is estimated as an indication of a

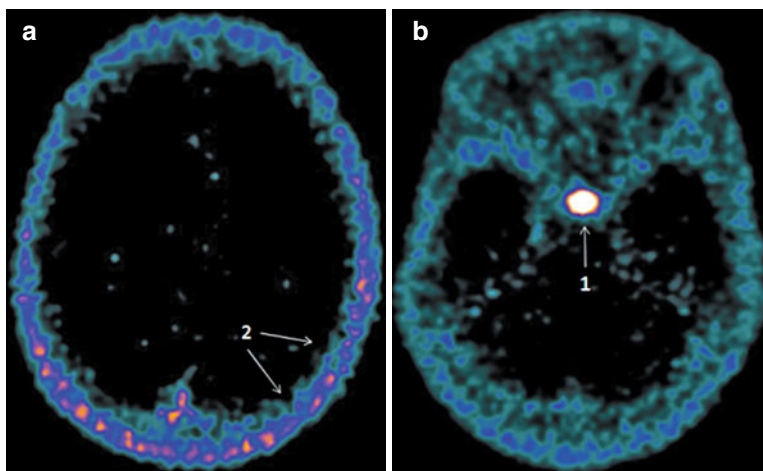


Fig. 19.3 Normal brain distribution of ^{68}Ga -DOTATOC. Physiological uptake (**a**, **b**) is detected in the hypophysis (1) and aponeurosis (2)

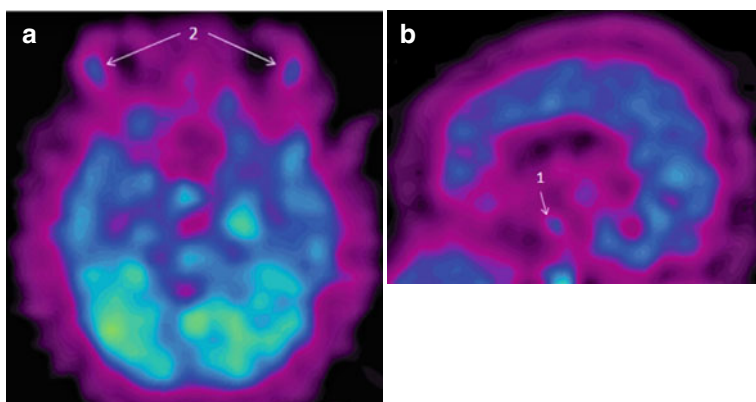


Fig. 19.4 Normal ^{11}C -SB distribution in the brain. Physiological uptake (**a**, **b**) is observed in the hypophysis (1) and tear glands (2)

malignant neoplasm, a T/NT ratio ≤ 0.5 indicates a benign neoplasm, and if the T/NT ratio value is 0.5–0.9 this is considered as borderline. Marginal T/NT ratio values do not provide any additional information for a diagnostic decision. Such patients need to be examined with other RPs or require a dynamic observation. If no clear foci of RP uptake are observed in the image in the projection of a solid mass, the maximum accumulation of RP within the area of a lesion visualized by MRI (CT) is assessed.

Possible use of ^{11}C -SB and ^{11}C -MET for differentiating tumors in degree of malignancy is under discussion. Low (background) level of uptake of these RPs in the cortex provides a highly contrasting image of neoplasms. A T/NT ratio ≥ 1.3 for

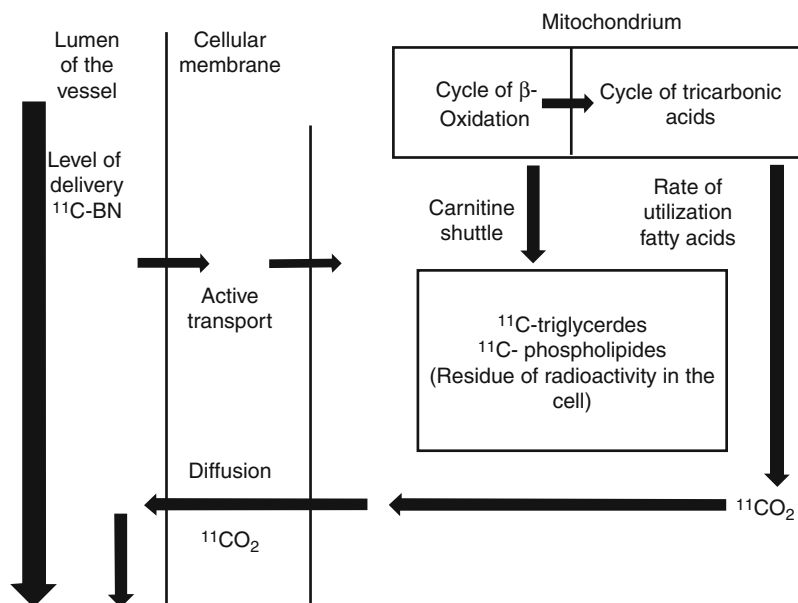


Fig. 19.5 ^{11}C -SB pharmacodynamics in tumor cells

^{11}C -SB and a T/NT ratio ≥ 2.5 for ^{11}C -MET are considered to indicate a malignant tumor, whereas a T/NT ratio ≤ 1.2 for ^{11}C -SB and a T/NT ratio ≤ 2.5 for ^{11}C -MET are estimated as signs of a benign tumor. It should be noted that using these T/NT ratio values for ^{11}C -SB and ^{11}C -MET is justified in gliomas.

The pharmacodynamic model for assessing metabolism of sodium butyrate in tumors (Fig. 19.5) does not significantly differ from the conventional model for fatty acids (Bergmann et al. 1996). Apparently the rate of fatty acid metabolism in tumors depends on their vascularization and on the activity of membrane and intracellular carrier proteins. In the first stage in the cycle of β -oxidation, ^{11}C -acetyl-CoA is generated from the labeled fatty acid. The second stage depends on the degree of tumor oxygenation: in case of oxygen deficiency, ^{11}C -triglycerides and ^{11}C -phospholipids are generated from ^{11}C -acetyl-CoA, which are taken up by tumor cells. If tumor oxygenation is not disturbed, in the Krebs cycle the metabolism of ^{11}C -acetyl-CoA occurs with the generation of water and $^{11}\text{CO}_2$.

The analysis of the activity-time curves in tumors in ^{11}C -SB PET includes determining the degree of their vascularization, the rate of fatty acid uptake, and the level of their metabolism (T/NT ratio), the fatty acid utilization rate, and the index of tumor oxygenation. The degree of vascularization in tumor is calculated as the ratio of the maximum radioactivity value in tumor focus to the intact cortex in the first minute (vascular phase). If the degree of vascularization is higher than 2.0, it is estimated as high (++), if it is from 1.5 to 2.0 it is considered to be

moderately high (+), from 1.0 to 1.5 it is estimated as lower and below 1.0 it is said to be low (−). The rate of uptake (UR) is the time of achieving the maximum radioactivity accumulation in tumor in the tissular phase (from the 2nd to 30th min). When the UR value is approximately 4 min, it is estimated as high, when the UR is more than 4 min, it is considered as low. UR seems to reflect the membrane activity of fatty acid transport in tumors. The level of metabolism of fatty acids in tumor is defined as the ratio of maximum values of accumulated radioactivity in the tumor to the radioactivity of the non-changed tissue (T/NT) in the tissular phase. The fatty acid metabolism rate is defined as the inverse ratio of the maximum value of radioactivity (MV) in the tissular phase of tumor to the value of radioactivity in it 30 min later (percentage). The average MV for malignant tumors makes up 20%. If $MV \geq 20\%$, it is estimated as high, if it is less than 20%, then it is said to be low. Some authors think that MV indirectly reflects the degree of oxygenation of neoplasm and speed of proliferative processes. Low MV in presence of high or elevated microcirculation indicates predominance of plastic processes in the tumor, which can indirectly testify its high proliferative activity. The rate of oxygenation is defined as the ratio of MV in a given tumor to the average MV (Kostenikov et al. 2006).

19.6 Clinical Use of PET in Neurooncological Patients

PET examination of the brain under suspicion of a solid mass is in all cases performed after a clinical examination of the patient and after MRI or CT with contrast enhancement. MRI or CT data in presence of structural changes provide a reason for implementing PET and are used in analyzing functional PET images.

The indications for performing PET in case of brain tumor suspicion:

1. Specification of the character of structural changes in the brain, detected by MRI or CT with contrast enhancement.
2. Choice of a representative site for biopsy in highly heterogeneous tumors and in cases when the formation does not accumulate contrast substance.
3. Determining the radicality of neurosurgical intervention, detecting residual tumors.
4. Assessment of the efficiency of conservative treatment according to the criterion of metabolic activity of tumor cells: complete metabolic response, partial metabolic response, stabilization or progress of the disease.
5. Evaluation of the dissemination of tumor processes in therapy planning.
6. Diagnosis and differential diagnosis of tumor relapses and radiation necrosis.
7. Detection of malignization of a benign brain tumor.

PET examination should begin with use of labeled amino acids (^{11}C -MET, ^{18}F -FET) or ^{11}C -SB, which has high sensitivity in detecting brain tumors. ^{18}F -FDG PET permits to detect only malignant tumors.

Pathologic uptake of the indicated pharmaceuticals in the area of lesion detected by MRI or CT is considered to be a PET indication of a neoplasm.

19.6.1 Diagnosis of Primary Malignant Tumors and Brain Metastases

Malignant neoplasms have the following scintigraphic signs: glucose, amino acid and fatty acid hypermetabolism, hypervascularization, nonhomogeneous accumulation of RP, multifocality, vagueness of image contours. It should be noted that the unidirectional nature of scintigraphic signs indicating the malignant character of a neoplasm may be used as additional information in complex clinical situations. For diagnostic decision making, the Accumulation index of RP in tumor can be used as a quantitative criterion, especially in cases of its isometabolism. T/NT ratios (tumor/contralateral area of the cortex) obtained in our research with use of different RPs in malignant, benign and non-tumor brain masses are listed in Table 19.2.

It is clear from Table 19.2 that there are significant differences in FDG T/NT ratio between malignant and benign tumors. When using SB T/NT ratio and MET T/NT ratio, differences are detected between tumors and non-tumor formations.

Malignant gliomas. Gliomas make up the majority of primary brain neoplasms. Gliomas are distinguished by their localization in deep sections of the cerebral hemispheres or in deep brain structures, invasive growth with expansion to adjacent structures or hemispheres. There is a direct correlation between the level of micro-circulation in gliomas and the degree of their malignancy. This accounts for the interconnection between the degree of malignancy and the level of accumulation in gliomas of certain RPs, like ^{11}C -SB and ^{11}C -MET (^{11}F -FET), whose uptake depends on the level of tumor vascularization. For ^{18}F -FDG, ^{11}C -SB and ^{11}C -MET,

Table 19.2 T/NT ratio in PET with different RP in patients with brain solid masses (our data)

Type of tumor	FDG T/NT ratio	SB T/NT ratio	MET T/NT ratio
Malignant tumors	1.4 ± 0.42	2.1 ± 0.63	2.4 ± 0.71
Glioblastoma	1.5 ± 0.47	2.1 ± 0.67	2.6 ± 0.45
Anaplastic astrocytoma	1.1 ± 0.23	1.6 ± 0.46	1.9 ± 0.69
Medulloblastoma	1.4 ± 0.53	2.4 ± 0.42	–
Anaplastic meningioma	1.3 ± 0.32	2.2 ± 0.56	2.9 ± 0.91
Cancer metastases to the brain	1.0 ± 0.51	2.3 ± 0.61	–
Benign tumors	0.5 ± 0.21	1.5 ± 0.8	2.1 ± 1.2
Benign astrocytomas	0.7 ± 0.09	1.2 ± 0.37	1.6 ± 0.15
Benign meningiomas	0.6 ± 0.14	2.2 ± 0.74	2.4 ± 0.91
Neurinomas	0.3 ± 0.13	1.2 ± 0.29	–
Pituitary adenoma	0.4 ± 0.09	2.1 ± 0.74	2.3 ± 1.04
Cholesteatoma	0.3 ± 0.13	0.5 ± 0.28	–
Dermoid cysts	0.3 ± 0.13	0.4 ± 0.14	–
Non-tumor formations	0.4 ± 0.20	0.4 ± 0.21	0.6 ± 0.29
Cerebral blood flow disorder	0.6 ± 0.17	0.6 ± 0.23	0.8
AVM	0.5 ± 0.27	0.6 ± 0.26	0.7 ± 0.35
Cysts	0.2 ± 0.08	0.4 ± 0.21	0.3

Table 19.3 Optimum threshold T/NT ratio values for excluding malignant gliomas

RP	T/NT ratios		Threshold T/NT ratios
	In 95% of cases in BG	In 95% of cases in MG	
^{18}F -FDG	<0.8	>0.9	≥ 0.9
^{11}C -MET	<1.8	>2.0	≥ 2.0
^{11}C -SB	<1.2	>1.6	≥ 1.3

MG malignant gliomas (GB and AA), BG benign gliomas

accumulation indices are described which can be used as criteria in the differential diagnosis of malignant gliomas (Table 19.3).

Glioblastomas (grade IV) are distinguished from other tumors by the high rate of metabolic processes combined with high metabolism of glucose, amino acids and fatty acids (Fig. 19.6). However, low (isometabolic and hypometabolic) glycolysis in glioblastomas is observed in more than 30% of cases. The levels of vascularization and of metabolism in glioblastomas depend on their histological form. In monster cell and isomorphous glioblastomas, the degree of vascularization and of metabolism is lower than in the multiform ones. A distinctive feature of glioblastomas is the presence of several confluent foci, vast areas of necrosis and cysts. Multifocality is not proper of glioblastomas. High level of amino acid and fatty acid metabolism enables convincing visualization of glioblastomas. Cases of false-positive ^{18}F -FDG or ^{11}C -MET PET diagnosis of glioblastomas are associated with diseases of an inflammatory nature, such as brain abscesses, vasculites, and encephalites. In some cases this problem can be solved under MRI examination or in delayed ^{18}F -FDG PET scanning. ^{11}F -FET also can be used for this purpose because it is not accumulated in inflammation foci and so permits to differentiate glioblastomas from abscesses (Floeth et al. 2007).

Besides that, in most cases these diseases significantly differ in clinical manifestations. False-negative diagnosis, when ^{18}F -FDG is used may be conditioned by diabetes in a decompensated form, marked atherosclerosis of brain vessels, tumor hemorrhages and marked peritumorous edema. The indicated pathologic states lead to reduction in the level of microcirculation and rate of metabolic processes in tumor, which should be taken into account in interpreting PET data.

Anaplastic (non-differentiated) astrocytoma (AA) is characterized by predominance of high amino acid and fatty acid metabolism rates over a relatively low level of glucose metabolism and moderately high vascularization. Visualization of AA of large size (more than 4–5 cm) with vast cysts and necrosis areas is often difficult in ^{18}F -FDG PET since the tumor image is ill-differentiated from surrounding ischemic brain tissues. In this situation fusion of PET and MRI images is needed for determination of the boundaries of the neoplasm and subsequent quantitative assessment of the metabolism speed within it (Fig. 19.7). At the same time, high metabolism of amino acids and fatty acids permits, as a rule, the distinct visualization of astrocytomas. Another characteristic feature of AA is their multifocality.

As for the characteristics of medulloblastoma, we can only mention its specific location in the cerebellar hemispheres as well as the fact that it usually

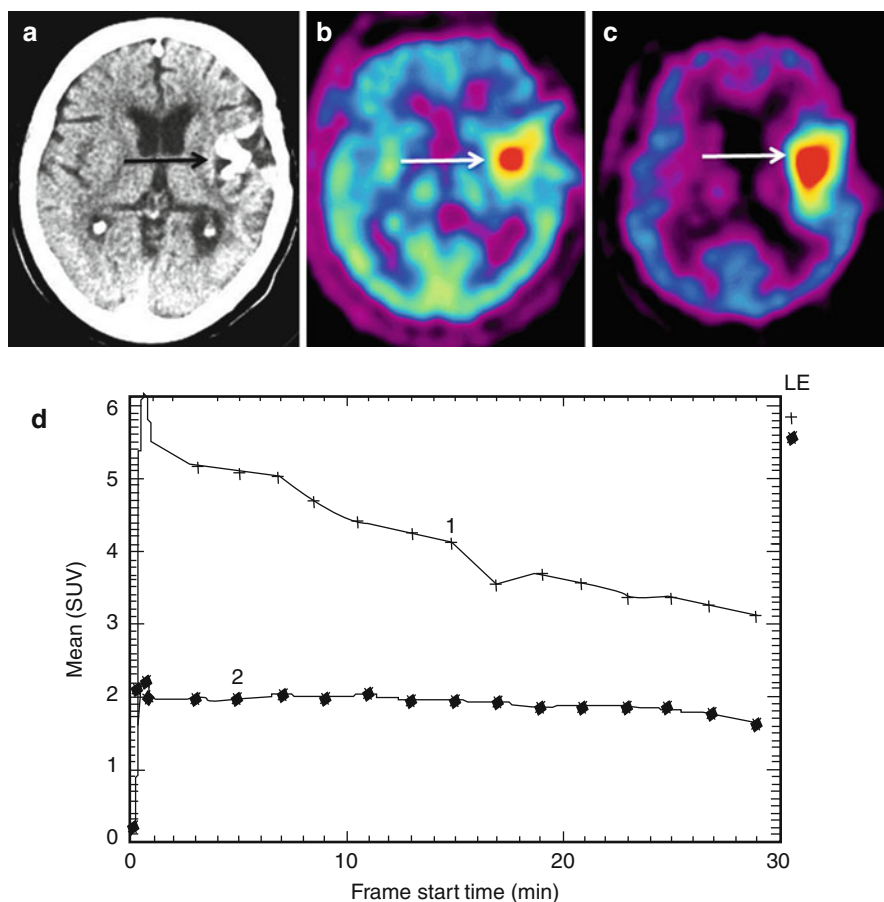


Fig. 19.6 ^{18}F -FDG and ^{11}C -SB PET before surgery of a multiform glioblastoma of the left parietal-temporal lobe. (a) CT detects tumor in the left parieto-temporal lobe. (b) ^{18}F -FDG PET reveals a focus of glucose hypermetabolism, T/NT ratio=1, 7. (c) ^{11}C -SB PET shows a focus of fatty acid hypermetabolism, T/NT index=2, 5. (d) Typical time-activity curve obtained in ^{11}C -SB PET in the malignant tumor (1) and contralateral brain area (2). The curve of the malignant tumor shows the neoplasms well perfused

develops in childhood. Otherwise these tumors do not differ scintigraphically from glioblastomas.

Atypical and anaplastic (malignant) meningioma. In anaplastic meningiomas, hypervascularization corresponds to high metabolism of glucose, amino acids and fatty acids, and to the rapid uptake and accelerated utilization of fatty acids (Fig. 19.8, 1–2). Atypical meningioma differs from anaplastic meningioma in glycolysis rate, which can range within large limits in atypical meningiomas, but on average is lower than in anaplastic meningiomas.

Meningiomas are as a rule convincingly diagnosed in MRI by their specific connection with the hard meninx and bone structures, their extracerebral localization

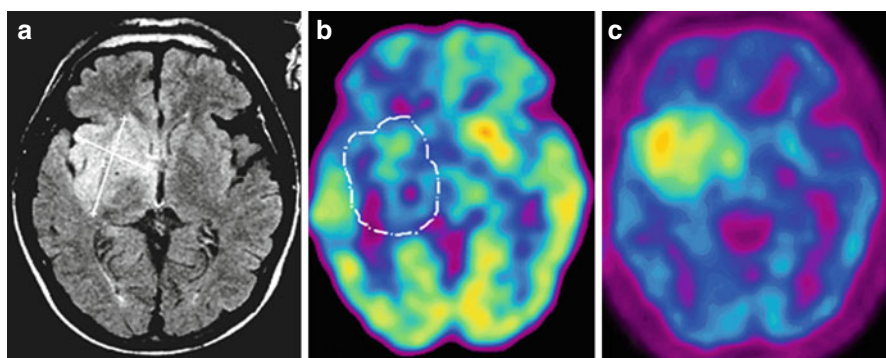


Fig. 19.7 ^{18}F -FDG and ^{11}C -SB PET before surgery of anaplastic astrocytoma of the right parieto-temporal lobe clearly visualized on MRI (STIR) (a). Lack of focal hypermetabolism on ^{18}F -FDG PET (b) and focal fatty acid hypermetabolism on ^{11}C -SB PET (c) suggest malignant nature of the tumor

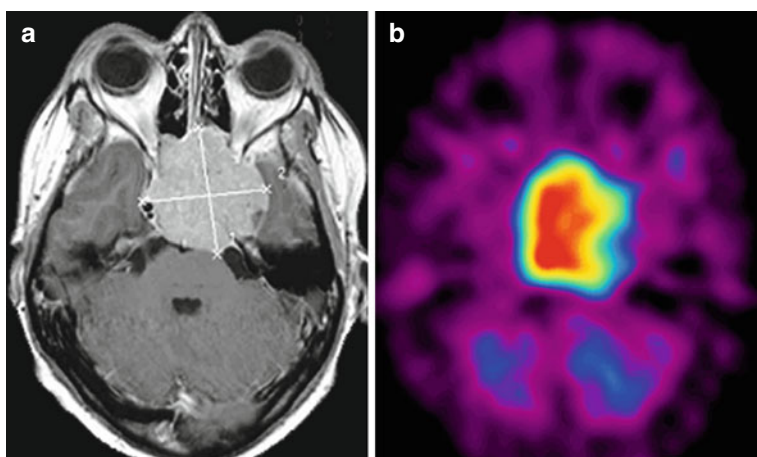


Fig. 19.8 Meningiosarcoma of the anterior cranial fossa visualized on. (a) MRI (T1 WI with contrast agent) with focal increase of fatty acid metabolism on ^{11}C -SB PET (b)

and marked contrast enhancement effect after introducing gadolinium-containing contrast agents. PET, as part of primary diagnosis, pursues the purpose of visualization and determination of degree of malignancy of meningiomas. It should be stressed that ^{68}Ga -DOTATOC PET-CT is highly efficient in assessing the dissemination of meningiomas, detecting their continued growth and relapses and determining degree of infiltration of structures adjacent to the tumor.

Brain metastases of extracerebral tumors. Cancer metastases (CM) from extracerebral tumors are characterized by high amino acid and fatty acid metabolism. At the same time, cancer metastases are as a rule hypovascular and have low glucose metabolism (Fig. 19.9). Cancer metastases are convincingly diagnosed in MRI or

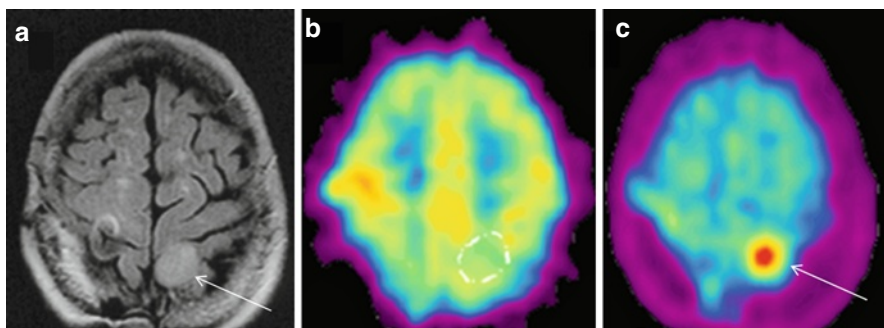


Fig. 19.9 Breast cancer metastasis in the left parietal lobe ($T_4N_2M_1$) clearly visualized on (a) MRI (proton density) with inhomogeneous tumor hypometabolism on ^{18}F -FDG PET (b) caused by low glycolysis and fatty acid hypermetabolism on ^{11}C -SB PET (c)

CT; consequently, PET for CM diagnosis is used only as a subsidiary method in rare unclear cases.

Examination of patients with metastatic brain lesion and undetected primary tumor often begins with differentially diagnosing metastases and glioblastomas. Glioblastomas, like metastases from extracerebral tumors, can have a multiple character due to intracerebral metastases, including those to the contralateral brain hemisphere. Contrast agent in MRI (CT) may be accumulated in the periphery of the brain. Such clinical situations cause difficulty in differentially diagnosing cancer metastases (CM). At the same time, CM are distinguished by an expansive growth, multiplicity of lesion, central necrosis, and glucose hypometabolism. In glioblastomas, these features are observed more seldomly than in CM (Table 19.4).

Benign tumors and non-tumor formations. The rate of metabolic processes and the level of vascularization may range within large limits. Glucose hypometabolism, homogeneous distribution of RP and distinct contours of the tumor focus are features of benign tumors.

Benign astrocytomas (BA) are characterized by low glucose metabolism, which makes difficult their differentiation from areas of disturbed cerebral blood circulation in strokes, whereas high amino acid and fatty acid metabolism in BA permits in most cases to solve this problem (Fig. 19.10). Benign oligodendrogliomas and pilocytic astrocytomas are an exception here; they are distinguished by high metabolism and accumulate ^{18}F -FDG, ^{11}C -MET and ^{18}F -FET in high amounts. Benign astrocytomas can malignize, so BA patients are subject to recurrent examinations in order to exclude malignization. (De Witte et al. 1996). As a criterion in detecting malignization, gradual stable or abrupt rapid increase of T/NT ratio in the tumor during dynamic observation is used. Increase in FDG T/NT ratio >0.9 or in MET T/NT ratio >1.7 indicates malignization (De Witte et al. 1996). Malignized benign tumors do not differ from primary malignant ones in their scintigraphic properties.

Benign meningiomas (BM) are also characterized by the high metabolism of AA (^{11}C -MET and ^{18}F -FET) and FA (^{11}C -SB) and by hypervascularization. At the same

Table 19.4 Differential-diagnostic signs of metastatic brain lesion and glioblastomas

№	Metastatic lesion	Glioblastomas
1.	Growth form Expansive	Infiltrative
2.	Multiple brain lesion occurs Often	Seldom
3.	Bilateral brain lesion occurs Often	Seldom
4.	Mass effect is marked As a rule	In presence of marked edema
5.	Central necrosis occurs In any tumor size	In large tumor size
6.	Accumulation of MRI contrast agent in the form of a “fringe” Usually	Seldom
7.	Regular oval or round form occurs Often	Seldom, in tumor size no less than 1–2 cm
8.	Localization Random	Cortex cerebri and deep brain structures

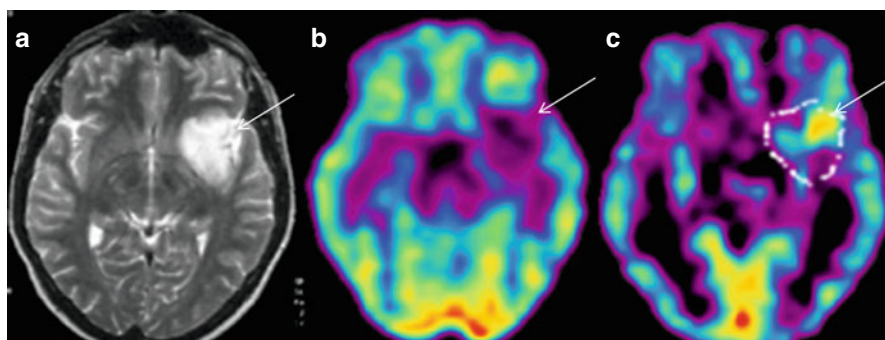


Fig. 19.10 Benign oligoastrocytoma in the left fronto-temporal lobe. The use of ^{11}C -SB (c) enables downsizing of the tumor mass as visualized on MRI (a). The hypometabolic character of (b) ^{18}F -FDG suggest benignancy of the lesion

time, the level of ^{18}F -FDG accumulation in BM is low (Fig. 19.11). Regardless of their degree of malignancy, meningiomas have a high level of somatostatin receptors and accumulate ^{68}Ga -DOTATOC in high amounts.

Tumors of degree-I malignancy (neurinomas, cholesteatomas and dermoid cysts) are characterized by low glucose, amino acid and fatty acid metabolism and by low vascularization. Therefore their visualization and identification are difficult, with the exception of pilocytic astrocytomas, which accumulate labeled glucose, amino acids and fatty acids in high amounts due to their heterogeneous structure. MRI or CT diagnosis of these tumors does not usually pose any problems.

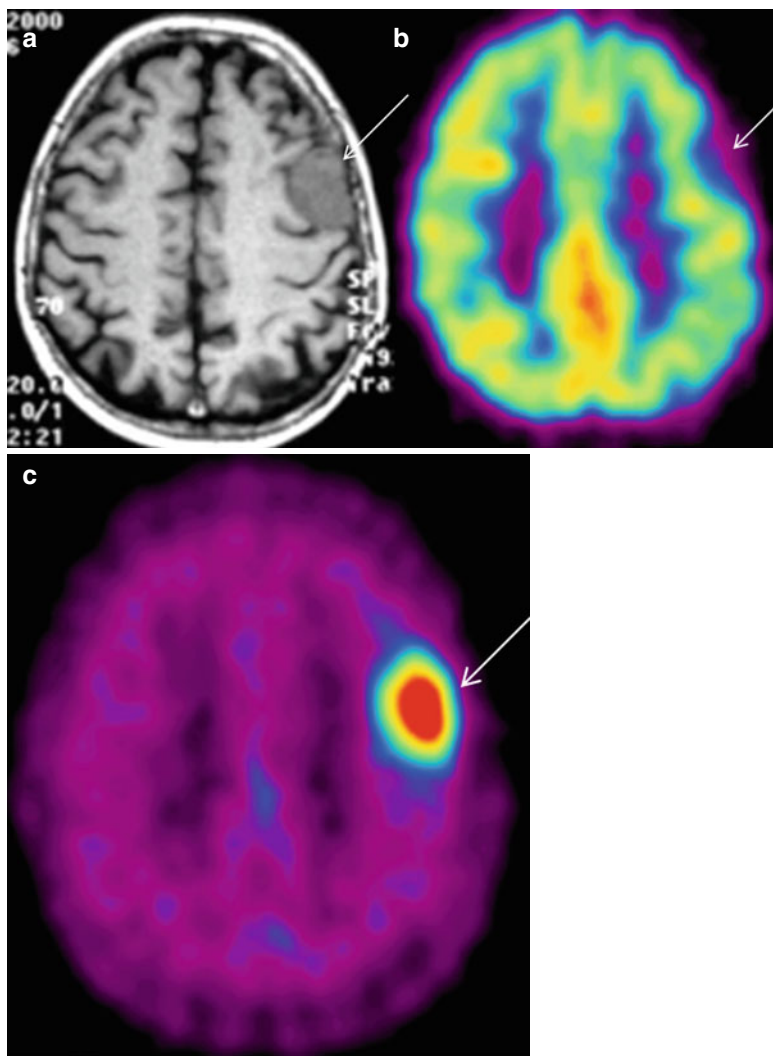


Fig. 19.11 Fibroblastic meningioma of the left fronto-parietal lobe clearly visualized on (a) MRI (T1-WI) with hypometabolism on (b) ^{18}F -FDG PET and hypermetabolism on (c) ^{11}C -SB PET suggesting benignancy of the lesion

Non-tumor brain formations. Areas of brain lesion in disturbed cerebral circulation are characterized by low vascularization, which corresponds to low metabolism of glucose, amino acids and fatty acids. Arteriovenous malformation (AVM) is distinguished from disturbed brain circulation (DBC) by extremely high vascularization. AVM is not distinguishable from DBC and SAH (subarachnoid hemorrhage) as its most frequent manifestation in other scintigraphic signs. At the same time, the diagnosis of AVM does not usually cause difficulty in the stage of MRI and

Table 19.5 Information value of PET with different RP in diagnosing primary malignant brain tumors and metastases

№	Examination	Sensitivity (%)	Specificity (%)	Diagnostic value (%)
1	^{18}F -FDG PET	80–86	80–93	80–92
2	^{11}C -MET PET	80–94	80–91	80–94
3	^{18}F -FET PET	93–95	96–99	97–98
Our data				
4	^{11}C -SB PET	90–93	80–90	81–93
5	^{18}F -FDG and ^{11}C -SB PET	90–94	81–94	82–95

angiography. Vascularization and metabolism in cysts are low or absent. Liquor cysts are ametabolic and avascular. In posttraumatic and post-operation cysts as well as in those developed as a result of DBC significant fluctuations of the rate of metabolic process can be observed. Therefore their differential diagnosis from DBC and benign tumors of the degree I is difficult and cannot be considered as grounded if only PET is used.

Data on the information value of PET with different RP in differential diagnosis of primary malignant brain tumors are shown in Table 19.5.

From the listed data it is clear that ^{18}F -FET PET has the highest informative value, approaching 100%.

Examinations with ^{11}C -SB and ^{18}F -FDG also appear to be promising in difficult differential diagnostic cases. Combined use of these RPs increases the informative value of PET examinations of the brain in detecting malignant neoplasms.

Compared with labeled amino acids, the fatty acid ^{11}C -SB after a single introduction permits additional diagnostic information to be obtained on vascularization, uptake rate and utilization of fatty acids. That is why ^{11}C -SB PET makes it possible to assess in detail the microcirculation and phases of metabolic processes in tumors. At the same time, the labeled acids ^{11}C -L-MET and ^{18}F -FET have higher T/NT ratio in benign tumors, especially in benign astrocytomas and consequently they have a higher sensitivity in detecting them than ^{11}C -SB.

19.6.2 Diagnosis of Continued Growth and Relapses of Neoplasms

Diagnosis and treatment of brain tumor continued growth is still a very important and yet rather difficult neurooncological problem. Suffice it to say that continued growth of tumors of the glial family is observed during the post-operation period in 90% of cases (Walker et al. 1979; Konovalov 1997). In spite of obvious advantages of MRI in diagnosing brain tumors, this method has significant limitations in the diagnosis of continued growth and relapses. For example, injury of the blood–brain barrier consequent on local therapy leads to the accumulation of contrast substance in the necrosis area, which is indistinguishable from tumor in MRI scans. The problem of differentiating tumor continued growth from necrosis is particularly urgent due to the development of modern therapeutic approaches (radiosurgery, brachytherapy, local chemotherapy, photodynamic laser therapy, nanotherapy) which provide

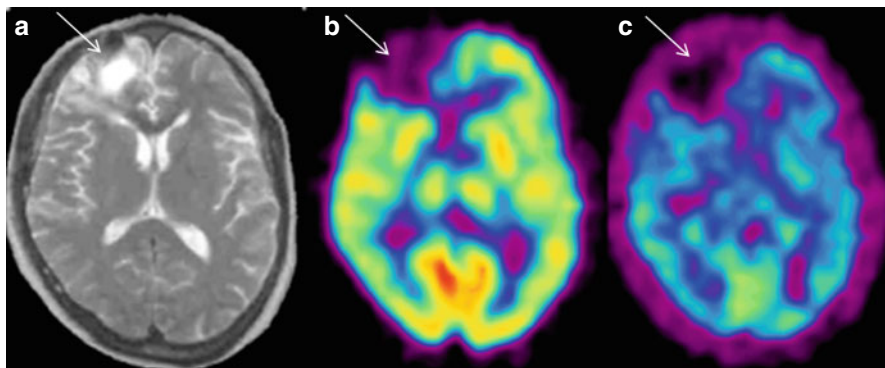


Fig. 19.12 State after surgery of the multiform glioblastoma of the right frontal lobe with post-surgical cyst on (a) MRI (T2-WI). The hypometabolism using (b) ^{18}F -FDG and (c) ^{11}C -SB PET serve as arguments against rest tumor or recurrence of a tumor

unique possibilities for efficiently influencing a restricted volume of an affected area of the brain.

Currently PET with the labeled amino acids ^{11}C -MET and ^{18}F -FET is most widely used for differentially diagnosing tumor relapses and post-radiation alterations. Most well-vascularized malignant gliomas are distinguished by high speed of accumulation of ^{18}F -FET, whereas in benign gliomas accumulation of this RP is slow (Pöpperl et al. 2006b). An important advantage of ^{18}F -FET in the diagnosis of continued growth and relapses is the fact that blood–brain barrier injury does not influence its uptake in brain tumors (Pöpperl et al. 2004; Rachinger et al. 2005). Moreover, Spaeth et al. (2004) have shown that ^{18}F -FET accumulates only insignificantly in areas of radiation necrosis.

After the extirpation of a tumor node in PET with an RP such as ^{11}C -MET, ^{18}F -FET, ^{18}F -FDG or ^{11}C -SB (Fig. 19.12), hypometabolic or ametabolic foci are visualized within the boundaries of non-changed brain tissues, these foci coinciding in size and localization with areas of post-operation cicatric-cystic alterations and cysts detected in MRI. At the same time in MRI implemented with contrast enhancement, a brief focal accumulation of contrast substance may be observed in the post-operation region, which is conditioned by blood–brain barrier injury and by disturbance of permeability of cell membranes in areas of cicatric-necrotic alterations (Fig. 19.13). Several months later, contrast agent accumulation in such areas as a rule is not detected.

The ratios tumor/non-changed cortex (T/NT) and post-operation region/non-changed cortex (results of our research) obtained in PET with ^{18}F -FDG and ^{11}C -SB in patients with suspicion of continued growth of malignant gliomas are shown in Table 19.6. It is clear from the table that when a tumor node is removed, hypometabolic accumulation both of ^{18}F -FDG and of ^{11}C -SB is observed within nonchanged tissues in the post-operation region. The average values of accumulation indices in the post-operation area in a group of patients without signs of continued growth are 0.45 for ^{18}F -FDG and 0.67 for ^{11}C -SB.

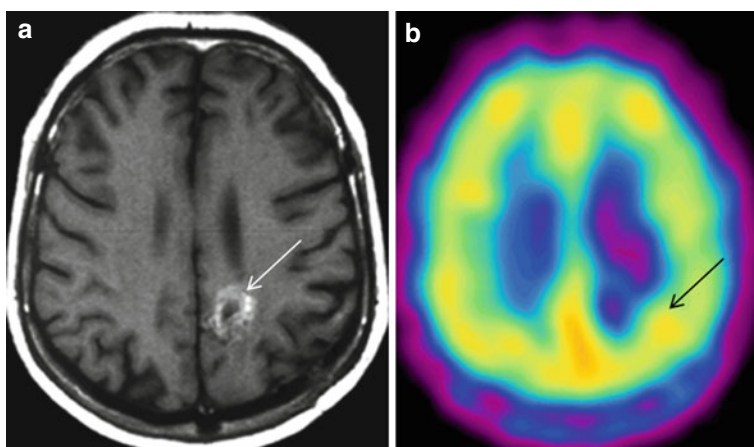


Fig. 19.13 State after surgery of anaplastic astrocytoma of the left parietal lobe with postsurgical cyst with contrast enhanced rim on (a) MRI (T1-WI) and no focal uptake on (b) ^{11}C -SB PET suggesting no residual tumor or recurrence

Table 19.6 T/NT ratios obtained in ^{18}F -FDG and ^{11}C -SB PET in patients with continued growth of malignant gliomas (our data)

Nosological form and volume of surgical intervention	^{18}F -FDG T/NT ratio	^{11}C -SB T/NT ratio
Glioblastoma		
Post-operative area/unchanged cortex	0.43 ± 0.11	0.58 ± 0.23
Continued growth/unchanged cortex	1.39 ± 0.69	1.57 ± 0.28
Anaplastic astrocytoma		
Post-operative area/unchanged cortex	0.47 ± 0.17	0.75 ± 0.27
Continued growth/unchanged cortex	1.21 ± 0.47	1.51 ± 0.47

POA stands for post-operative area, CG means continued

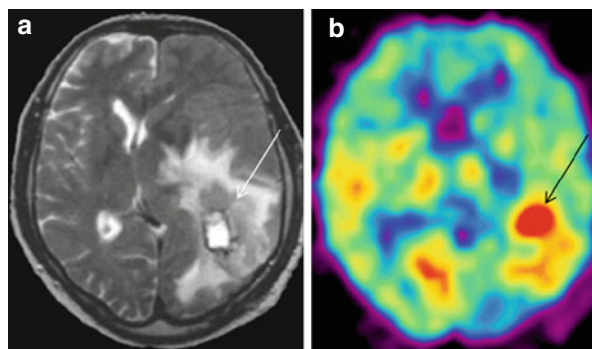
In the presence of continued growth of malignant tumors, the hypermetabolism of AA and FA is detected in almost 100% of cases, whereas glucose hypermetabolism is only in 60–70% (Fig. 19.14).

False-negative PET conclusions are caused by attempts to diagnose with PET tumors having dimensions less than 5–6 mm, which is due to restrictions imposed by the resolving capacity of PET scanners.

The few cases in which MRI does not permit the detection of continued tumor growth are observed in cases of disturbed microcirculation caused by the tumor being compressed by a post-operation cyst or by a marked edema, especially in the posterior cranial fossa.

In foci of continued tumor growth, high metabolism rate is observed, the T/NT ratio being 1.12 for ^{18}F -FDG and 1.57 for ^{11}C -SB. Continued growth foci differ significantly in these values from cicatric-necrotic and cystic post-operation alterations in examinations both with ^{18}F -FDG ($p < 0.0001$) and with ^{11}C -SB ($p < 0.0001$).

Fig. 19.14 Anaplastic astrocytoma of the left parieto-temporal area with perifocal oedema on (a) MRI (T2-WI) and (b) fatty acid hypermetabolism on ^{11}C -SB PET confirming tumor size and its malignancy



At the same time, significant differences in T/NT ratio between malignant tumors in the presence of continued growth are not detected in PET with ^{18}F -FDG ($p > 0.3$) and ^{11}C -SB ($p > 0.4$). (Skvortsova et al. 2001a; Kostenikov et al. 2006).

So we can state that some experience has already been accumulated in radiodiagnosis of neoplasms and other solid brain masses, which permits to differentiate pathologic processes, to precisely determine their localization, situation, form, structure and size.

19.6.3 Capabilities of PET in Treatment Efficiency Evaluation

Modern methods of radiotherapy of different brain tumors are intended for a target-directed high-dose irradiation of tumors with minimum radiation exposure of surrounding areas of the brain (Wurm and Plotkin 2008). A precondition for using stereotactic high-dose radiotherapy is usually precise differentiation of tumor tissue from perifocal edema and cicatric alterations. For radiotherapy planning in neurooncology, MRI with contrast enhancement is usually used. However, MRI has limited capabilities in determining tumor volume and metabolic activity. Currently PET with labeled amino acids is widely used for the planning and efficiency evaluation of radiotherapy of brain tumors. Available data convincingly demonstrate the high informative value of PET in determining tumor dissemination and in planning stereotactic radiotherapy and radiosurgery (Pauleit et al. 2005; Plotkin et al. 2006). Owing to the use of the DICOM format in modern PET-CT scanners, different modality images are compatible with most systems of radiotherapy planning. On the basis of PET data, the location, extension and boundaries of the viable part of a tumor are determined, its volume and plan of irradiating are developed, which are subsequently transferred to CT (MRI) images.

Besides labeled amino acids, a number of RPs have been recently suggested which are potentially of interest for brain tumor radiotherapy planning.

They are: the membrane-formation marker ^{18}F -choline, the proliferation marker ^{18}F -fluoroethylimidine (^{18}F -FLT), markers of hypoxia ^{18}F -FMISO and ^{18}F -FAZA, and the somatostatin receptor marker ^{68}Ga -DOTATOC (Henze et al. 2001).

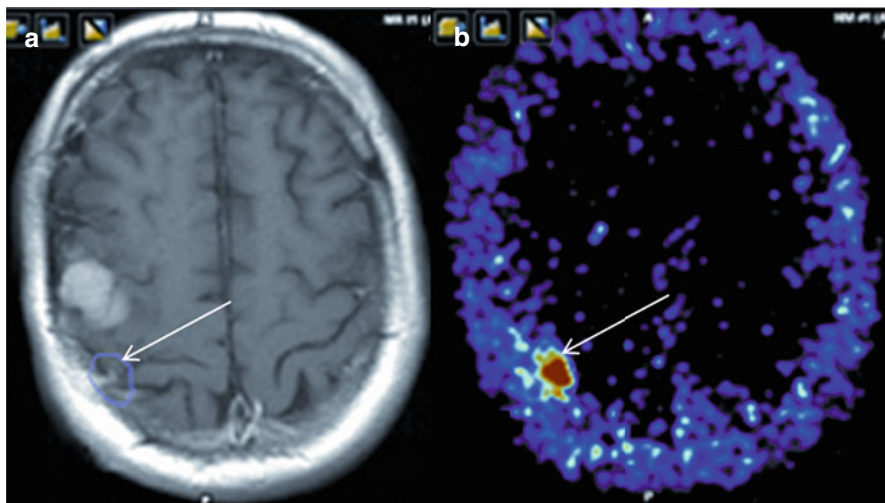


Fig. 19.15 Atypical multifocal meningioma of the right parietal lobe. State after multiple tumor resection. After contrast agent application enhancement in the area of surgery on (a) MRI (T1-WI). The additionally performed ^{68}Ga -DOTATOC-PET (b) confirmed relapse in the area of scar

A prospective study comparing the value of ^{68}Ga -DOTATOC PET-CT with contrast-enhanced MRI planning stereotactic radiotherapy of meningiomas has convincingly shown the advantages of the former over the latter (Fig. 19.15). PET-CT permitted correction of the MRI-determined irradiation volume in 58% of cases. The method of ^{68}Ga -DOTATOC PET-CT is also informative in cases of infiltration of the bone structures of the skull base and in multimodal meningiomas (Plotkin et al. 2007). Currently a number of RPs are used for treatment efficiency evaluation: ^{11}C -MET, ^{18}F -FET as well as ^{18}F -FDG and ^{11}C -SB (Fig. 19.16). ^{18}F -FET PET is considered to be the most promising of them (Grosu et al. 2006).

There is an inverse correlation between the life span of patients and glycolysis rate in tumor which is determined by FDG T/NT ratio and can be used for prognosis of the clinical course. A high initial level of glucose metabolism in a malignant tumor is estimated as an unfavorable prognostic factor (Spence et al. 2002).

Floeth et al. (2007) have detected prognostically significant features of ^{18}F -FET PET and MRI which permit to objectify the outcome of disease. In a patient group with tumors clearly circumscribed in MRI scanners, in which ^{18}F -FET uptake was not observed, the survival rate was 60 months, whereas in a patient group with clearly circumscribed but accumulating ^{18}F -FET formations it was only 38 months. The combination of diffuse tumor detected in MRI with ^{18}F -FET uptake proved to be the most unfavorable prognostic sign (Floeth et al. 2007).

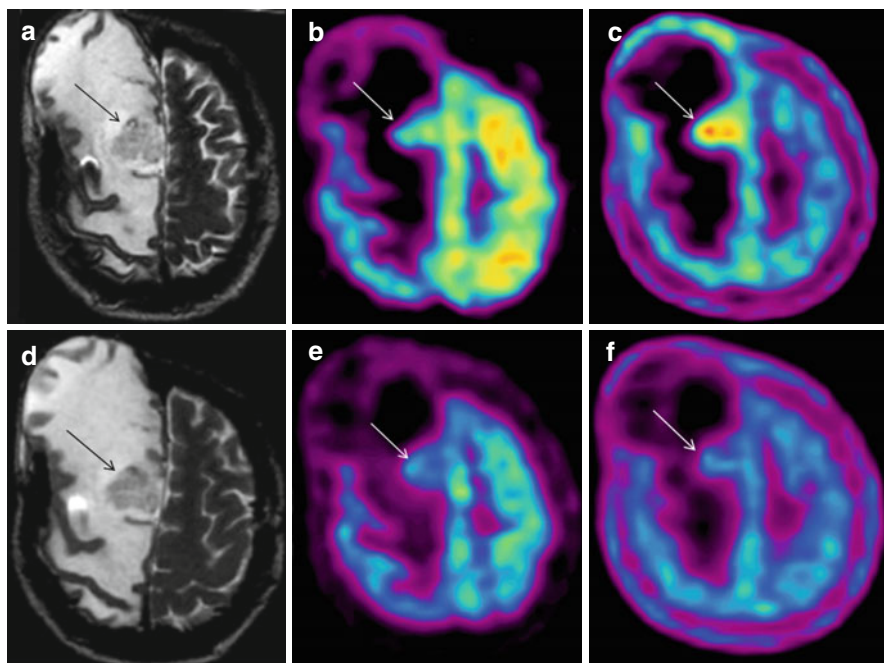


Fig. 19.16 Anaplastic astrocytoma in the right frontal lobe. (a, b, c) – before and (d, e, f) – after first cycle of chemotherapy. In contrast to (a, d) MRI and (b, e) ^{18}F -FDG PET only (c, f) ^{11}C -SB PET shows decrease of fatty acid metabolism suggesting effectiveness of the applied chemotherapy

The optimum moment for implementing PET scanning and the threshold values of changes in tumor have to be determined in future research.

19.6.4 Using PET in Biopsy Planning

The development of computer methods of fused visualization has enabled the integration of PET into the process of planning of radiotherapy and stereotactic biopsy.

A distinctive feature of gliomas is their heterogeneity: often benign areas of tumor adjoin areas of anaplasia (Vaquero et al. 2000). In order to determine the degree of malignancy of gliomas MRI with contrast enhancement is widely used. In this process, focal accumulation of contrast agent (Gd-DTPA) is considered as a sign of malignancy. At the same time, we know that in 40–45% of cases tumors not accumulating contrast substance in MRI have histological signs of anaplasia (Leeds and Jackson 1994; Ginsberg et al. 1998).

The correctness of the histologic diagnosis depends on the accuracy of biopsy; when planning the latter, the problem of choosing a representative area of tumor

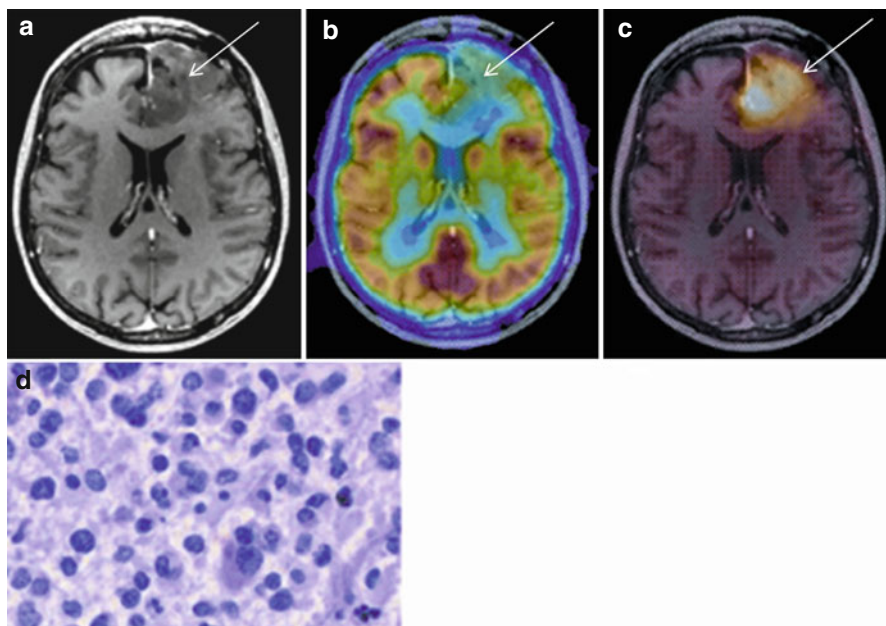


Fig. 19.17 Choice of tumor site in biopsy planning according to ^{18}F -FDG and ^{18}F -FET PET and MRI data. Anaplastic astrocytoma of the left frontal lobe. (a) MRI (T1-WI with CE): tumor is not visualized. (b) ^{18}F -FDG PET: tumor is not visualized, there is an inhomogeneous hypometabolic area in tumor projection. (c) ^{18}F -FET PET fused with MRI: a focus of RP uptake is detected. (d) Histologically mitoses and signs of nuclear pleomorphism, characteristic for anaplastic astrocytoma

becomes apparent (Fig. 19.17). A probability of mistake exists even in case of tumor resection, since only a part of it is accessible for histological examination, with considerable areas of neoplasm not being examined.

^{18}F -FDG PET was the first to be suggested for choosing the optimum site for biopsy of brain formations (Levivier et al. 1995) and is still used for this purpose, also in automated stereotactic navigation systems (Fig. 19.18). However, in recent years PET has not been considered as the method of choice in biopsy planning because more than 30% of malignant gliomas do not accumulate glucose in high quantities (Stockhammer et al. 2007). PET with labeled AA (^{11}C -MET or ^{18}F -FET, Fig. 19.19) has proved to be most efficient in biopsy planning and in visualizing anaplastic areas of mixed gliomas (Pirotte et al. 2004). A focus with maximum accumulation of RP is the optimum site for tumor biopsy.

Integration of PET into the procedure of stereotactic or intraoperative biopsy planning has been shown to be justified in the absence of or due to questionable results of contrasting in tumor in MRI. This approach is confirmed by data obtained by Roessler et al. (2007).

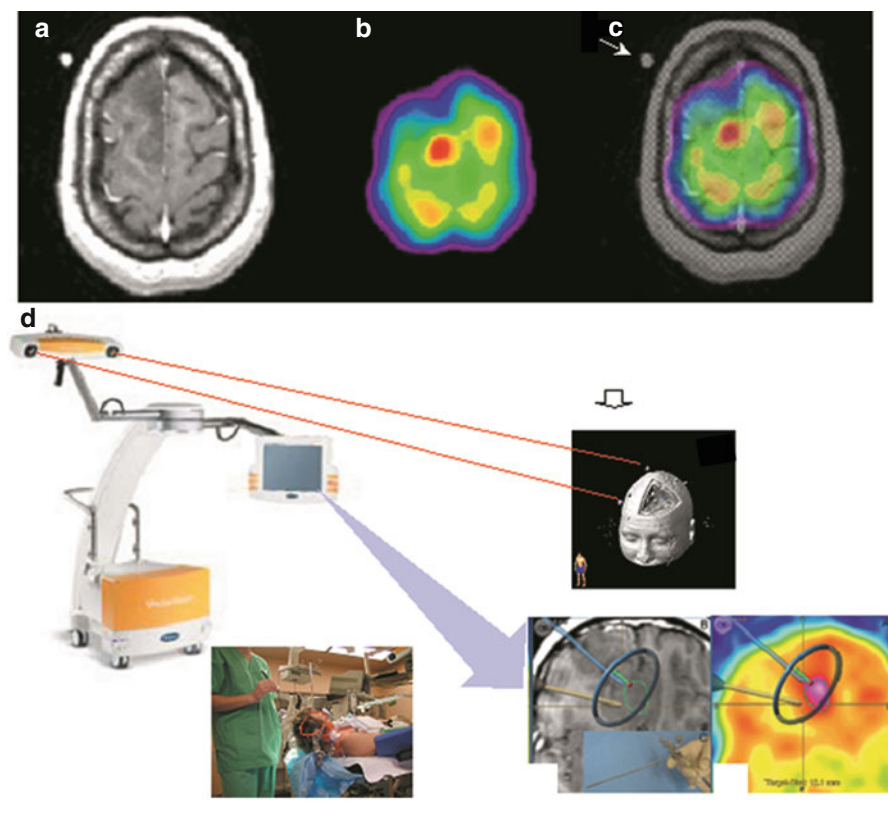


Fig. 19.18 Technique of using ^{18}F -FDG PET in planning and performing stereotactic biopsy. A retrospective fusion of (a) MR image with (b) ^{18}F -FDG scan is done as well as (c) visual analysis of the fused image with participation of the radiologist and of the neurosurgeon. Then PET and MRI images are transferred in the electronic form to the neurosurgical navigational system. With help of detectors the navigational system is combined with preimplanted subcutaneous markers and their position in the stereotactic coordinate systems determined. Coregistered PET and MRI images are projected to the monitor of the navigational system in the operating room. The neurosurgeon determines the position of the operative probe in PET and MRI images in the real time operation mode and intakes the sample from the tumor site with the highest RP uptake

19.6.5 Role of PET in the Development of Innovative Therapeutic Approaches

The ability of PET to visualize tumor metabolism makes this method an inestimable tool for the planning and efficiency evaluation of innovative approaches to brain tumor therapy. For example, ^{18}F -FET PET permits to efficiently assess results of local thermotherapy with magnetic nanoparticles.

The method is based on controlled hyperthermia of the tumor, into which metal-containing nanoparticles are preimplanted by means of a stereotactic system

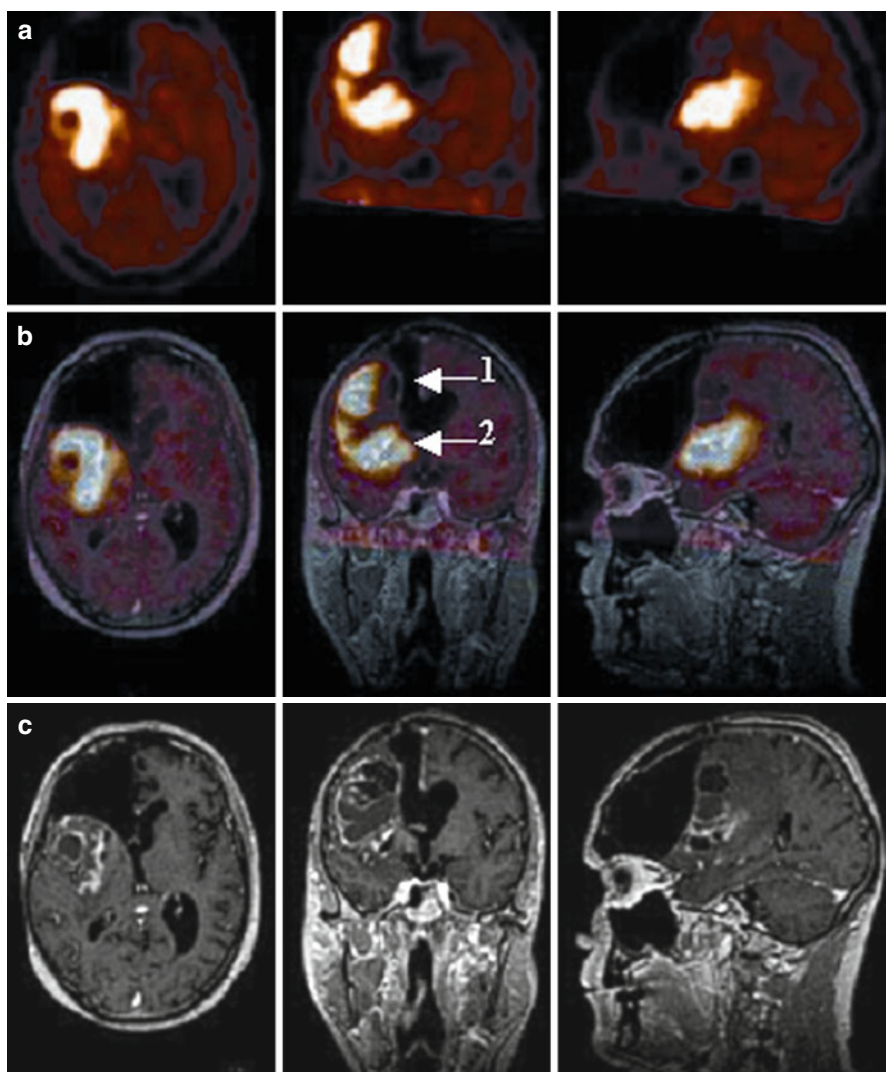


Fig. 19.19 ^{18}F -FET PET for planning radiotherapy of a glioblastoma of the right parietal lobe. (a) ^{18}F -FET PET data in three projections: an inhomogeneous focus of glucose hypermetabolism is detected. (b) In ^{18}F -FET PET, fused with MR image, necrosis areas (1) are differentiated from viable tumor areas (2). (c) In MRI (T1-WI with contrast agent) recurrent glioblastoma is visualized

(Gneveckow et al. 2004). Particular importance of ^{18}F -FET PET for nanotherapy efficiency evaluation is due to the fact that artifacts caused by the implantation of metal-containing particles do not allow the use of MRI or CT for this purpose (Plotkin et al. 2007). Radioimmunotherapy with use of monoclonal antibodies BC-4 has been successfully tested in examining patients with gliomas of WHO grades

III-IV (Pöpperl et al. 2002). It has been showed that ^{18}F -FET PET is informative in evaluating the efficiency of radioimmunotherapy (Pöpperl et al. 2006b) and permits clear discrimination of relapses from necroses.

So it is evident that PET is a highly efficient additional method of examination which is promising for wide use in neurooncology. Until recently ^{18}F -FDG remained the main diagnostic RP. However, its detected features (high asymmetric accumulation in the cortex, absence of uptake in some malignant tumors, and vice versa, and high accumulation in some benign formations) suggest the necessity of using other known tumor-seeking RPs and motivate synthesis and introduction into clinical practice of specific tumor-seeking pharmaceuticals. ^{18}F -FDG still retains some importance at the stage of determining tumor malignancy and prognosis of the course of tumor process, as well as in that of evaluating treatment efficiency. However, the main problems of clinical importance, such as the choice of a representative area for biopsy, determination of residual tumor, assessment of tumor dissemination, and detection of relapses, are currently solved by PET with labeled amino acids. ^{11}C -SB has proved to be also promising for solving these problems.

The prospects of further development of nuclear medicine are associated with the appearance and introduction into clinical practice of multimodal apparatuses such as PET-CT. Today, PET-CT is efficiently used in neurooncology in stereotactic interventions, in planning and in the evaluation of treatment efficiency. For example, PET-CT with the somatostatin receptor marker ^{68}Ga -DOTATOC has proved to be efficient in diagnosing relapses and in planning radiotherapy of meningiomas.

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Part III

Other Diagnostic Uses of PET

20.1 Introduction

Cardiovascular diseases are known to be the most frequent cause of disability and death in the employable population of the developed countries. In Russia, cardiovascular pathologies account for 55% of deaths. Most common (47%) among these diseases is coronary heart disease (CHD) (Vyalkov 2002; Oganov and Ya 2002). In Western Europe, the USA, Canada and Australia, mortality from ischemic heart disease has displayed a tendency to decrease over the last several decades. On the contrary, in Russia its growth is being observed. According to the expert committee of the Russian scientific society of cardiologists (2004), only 40–50% of the people who suffer from CHD are aware of their disease and receive adequate treatment, while in 50–60% of cases the disease remains undetected. In this light, it is obvious that improving early diagnosis of cardiovascular diseases with the aid of modern radiological methods can be of significant use in increasing the efficiency of secondary prevention of this pathology. Unfortunately, there still remains the idea in practical cardiology that selective coronography is the “gold standard” in diagnosing ischemic heart disease, since this method provides information on the anatomy of the coronary channel. Meanwhile this technique represents only the state of the intraluminal contour of coronary arteries and does not permit to thoroughly assess the functional significance of coronary stenoses. In addition, the procedure is invasive and may induce a number of complications, the most dangerous of them being hemorrhage from the area of puncture of femoral artery or damage of atherosclerotic plaques in the coronary artery orifices, which can entail embolism and provoke acute coronary syndrome with all consequences up to the lethal outcome.

Diagnosing CHD by means of routine noninvasive methods of examination (including electrocardiography, loading electrocardiography [ECG] tests [veloergometry and treadmill test], Holter monitoring and stress-echocardiography) is based on the alteration of the terminal part of the ventricular ECG complex, left-ventricular systolic and diastolic dysfunction, rhythm and conduction disorders which can result from transient decrease in myocardial blood flow. Presently the

frequency of false-positive and false-negative results, as well as questionable results, is well-known to be high for ECG stress tests (Belenkov and Ternovoy 2007). Thus, the necessity of improving noninvasive examination methods facilitating early diagnosis of cardiovascular diseases is evident now. The intensive development of modern technologies and improvement of computer techniques over the last two decades have promoted the appearance of substantially new noninvasive methods of examining the cardiovascular system, in particular coronary hemodynamics. These methods have significantly increased the efficiency of examining patients with CHD. Now different radiological techniques are used for studying myocardium perfusion, such as contrast echocardiography, MRI, SPECT, myocardial scintigraphy, etc.; however, PET is the most reliable method (Lishmanov and Chernov 2004; Phan 2004; Schelbert 2004; Belenkov and Ternovoy 2007; De Kemp et al. 2007).

It is established that PET made possible the study of coronary hemodynamics, biochemical processes in cardiomyocytes, the state of cardiac autonomic innervation on different levels of neurotransmission neurogenic transmission, angiogenesis, apoptosis, etc. under normal physiological conditions and in different pathological states. In the international literature there are many studies on the diagnostic capacities of PET in cardiovascular diseases (Gould 1999; Schelbert 2004; Kaufmann and Camici 2005; De Kemp et al. 2007). These studies show an utterly important role of PET in determining the extension and severity of ischemic heart disease, in early detection of microvascular pathology in persons with cardiovascular risk factors, as well as in diagnosing viable myocardium and in evaluating the efficiency of conservative therapy. PET of the heart with different radiopharmaceuticals (RPs) labeled with positron emitting radionuclides has been performed in the PET center of the Russian Scientific Center for Radiology and Surgical Technologies since 1997. Much experience has been accumulated in PET examinations of the heart in patients with CHD and noncoronary pathology. The present chapter is based on generalized worldwide experience of using PET in cardiological practice as well as on the results of our own studies.

20.2 Technical and Methodological Aspects of PET in Assessing Myocardial Perfusion

20.2.1 Cardiac Blood Supply and Coronary Blood Flow Regulation

The blood supply of the heart is carried out by the left and right coronary arteries departing from the initial part of the aorta above semilunar valves. The left coronary artery starts from the left posterior sinus and goes down towards the anterior longitudinal fissure. It is a wide but short trunk 10–11 mm long, which divides into anterior descending and circumflex branches. In rare cases one or two arteries depart additionally from the trunk of the left coronary artery; they are called intermediate. The anterior descending branch, or anterior interventricular branch as it is sometimes called, is a direct continuation of the left coronary artery and is situated in the anterior longitudinal cardiac gap going from the basal parts to the cardiac apex.

Sometimes it bends at the apex and passes to the inferior surface of the heart. Several (usually two) diagonal branches depart at sharp angle from the descending branch and go along the anterior surface of the left ventricle; they can reach the lateral wall. Besides that, septal branches depart from it. The anterior descending branch lies all along on the surface of the heart and is covered with epicardial fatty tissue. In some cases the artery plunges into the depth of the myocardium and forms short (up to 2 cm) muscular bridges. The circumflex branch of the left coronary artery departs virtually orthogonally from the trunk, passes in the transverse fissure up to the blunt edge of the heart, rounds it and passes to the posterior wall of the left ventricle. The right coronary artery originates in the anterior sinus and is situated deeply in fatty tissue on the right of the pulmonary artery. The artery goes around the heart along the right atrioventricular fissure, passes to the posterior wall, reaches the posterior longitudinal fissure and then goes down to the cardiac apex in the form of the posterior descending branch.

The anterior descending branch of the left coronary artery supplies with blood the anterior left-ventricular wall and sometimes the anterior part of the interventricular septum, the anterior papillary muscle of the left ventricle and sometimes that of the right ventricle. The circumflex branch nourishes the lateral and posterior walls of the left ventricle, the anterior and posterior papillary muscles and in part the sinus node. The right coronary artery supplies with blood the anterior right-ventricular wall, right-ventricular papillary muscles, the posterior right-ventricular wall, the inferior and in part the posterior left-ventricular walls and posterior part of the interventricular septum and sinus node. It should be noted that the blood supply territory of the anterior and lateral parts of the heart is rather stable and is not subjected to significant deviations, whereas the territory of arteries nourishing the posterior or diafragmal heart surfaces is very variable and depends on the type of coronary blood supply. It is accepted to distinguish three main types of coronary blood supply: the left, right and balanced supplies. In the left type of blood supply, the left atrium, all the left-ventricular segments, interventricular septum and, partially, the posterior wall of the right ventricle are nourished by the branches of the left coronary artery. In the right type of blood circulation, most segments of the heart, namely the right atrium, the right ventricle, interventricular septum, inferior and posterior walls of the left ventricle, posterior left papillary muscle and partially the apex, are nourished from the territory of the right coronary artery. The balanced type of blood circulation is characterized by uniform blood supply of the heart from the territories of the left and right coronary arteries.

The blood supply of the left atrium, left ventricle including both papillary muscles and the anterior part of the interventricular septum occurs through the left coronary artery. The right atrium, right ventricle and the posterior part of the interventricular septum are supplied with blood by the right coronary artery. Numerous small arteries depart from coronary arteries into the depth of the myocardium and form anastomoses with one another in all the cardiac layers. Unlike the arteries of the skeletal musculature, coronary arteries are characterized by high tensility; therefore, in presence of higher systemic arterial pressure, the myocardial blood flow increases four- to five-times more than in peripheral arteries. The capillary network in the cardiac

muscle is very thick, the capillary number per unit of weight here is three- to four-times as large as that in the skeletal musculature. The outflow of venous blood from the left coronary artery system enters the coronary sinus, from which venous blood enters the right atrium. As for the right coronary artery system, venous blood arrives directly to the right atrium from it. The normal pumping ability of the heart is ensured by adequate coronary blood flow. Higher myocardial oxygen demand due to exercise or emotional stress is normally accompanied by a rise in blood inflow on account of vascular vasodilation. High basal tone of coronary arteries, combined with different factors of neurohumoral regulation, provides vasodilatation reserve, which is the main mechanism of increasing blood inflow to the myocardium. Under normal physiological conditions, no signs of coronary insufficiency are observed under physical load of any level, even very high intensity.

Coronary blood flow, especially in subendocardial parts of the heart, is characterized by its dependence on the phase changes of the cardiac cycle, since the perfusion gradient in the vessels of the working heart is determined not only by difference between arterial tension in the input and venous tension in the output but also by cyclically changing pressure values in different parts of the heart. Myocardial blood supply is known to take place during diastole, when the tension of the myocardial wall is not high. During systole the cardiac blood flow decreases by roughly 80%. The value of diastolic pressure in the aorta is the determining factor for coronary blood flow. A decrease in diastolic pressure leads to a reduction in myocardial blood flow, while its increase augments the afterload on the left ventricle, inducing a rise in myocardial oxygen demand.

The regulation of coronary hemodynamics is a complex multicomponent process and it occurs by means of metabolic neurohumoral and myogenic mechanisms (Barabanov et al. 2001).

The metabolic regulation of coronary vascular tone is based on the so-called adenosine hypothesis. Physical load is accompanied by a higher frequency and intensity of systole, which results in high consumption of adenosine triphosphoric acid (ATP), the main source of energy of the cell. Adenosine reacts with A₂-purine receptors of the smooth muscles of arteriolar vascular wall, inducing their relaxation and correspondingly direct vasodilatation and elevated myocardial blood flow (Nees 1989; Kaufmann and Camici 2005).

Nervous regulation is carried out by both sections of the autonomic nervous system. Smooth-muscular cells of coronary arteries contain α 1- and β 2-adrenoreceptors and M-cholinoreceptors. Alpha2-adrenoreceptors are concentrated on the surface of endotheliocytes covering the interior surface of coronary arteries. Endothelium is known to play a crucial role in vascular tone regulation. The decisive role in this process belongs to nitric oxide formed in the endothelium, which, when entering the vascular lumen, has a vasodilating effect. Physical or emotional load induces the activation of the sympathetic autonomic nervous system, an increase in frequency and intensity of systoli and consequently a rise in myocardial oxygen demand. Reacting with α 2-adrenoreceptors of endotheliocytes, catecholamines stimulate the release of nitric oxide. Increase in concentration of nitric oxide on the surface of the vascular wall counterbalances the vasoconstrictive effect

Table 20.1 Comparative characteristics of RP for assessing myocardial perfusion

Isotope	$T_{1/2}$ (min)	Production	RP
^{15}O	2.04	Cyclotron	^{15}O -water
^{13}N	9.8	Cyclotron	^{13}N -ammonia
^{82}Rb	1.3	Generator	^{82}Rb -chloride
^{62}Cu	9.7	Generator	^{62}Cu -PTSM
^{38}K	7.7	Cyclotron	^{38}K -chloride

of catecholamines on α 1-adrenoreceptors of subjacent smooth muscular cells. In the presence of disturbed synthesis or nitric oxide release by endotheliocytes in reaction to catecholamine stimulation, the vasodilation of coronary arteries is absent or a paradoxical vasodilation is observed, which results in a disbalance between oxygen supply and myocardial need in oxygen and thereby to ischemia (Brunner et al. 2005). Other neuromediators, for example acetylcholine which influences the NO synthesis by means of M-cholinoreceptors, are able to cause vasoconstriction directly through contractions of smooth-muscular cells. However, under normal conditions of endothelial functioning the vasodilating effect prevails over the vasoconstrictive effect. Histamine is a strong vasodilator. Angiotensin and vasopressin for their part induce the narrowing of coronary arteries.

The myogenic regulation of coronary blood flow is considered to be based on the Ostroumov-Bayliss phenomenon, which is based on the interrelation between the contractile activity of the smooth musculature of the vascular wall and tensile force applied from without. This correlation is demonstrated in experimental studies on an isolated non-contracting heart. However, the physiological significance of myogenic regulation for the working heart is not sufficiently studied.

20.2.2 RPs for Assessing Myocardial Perfusion

The RPs used in PET are natural metabolites or their analogs. The introduction of radionuclides into them does not change their biological properties; this fact enables correctly assessing physiological and metabolic processes in cardiomyocytes. Short half-life periods permit the detection of fast reactions, which decreases by several fold the patient radiation exposure, shortens the examination duration and makes it possible to do repeated scans with short delay.

Isotopes and RPs for assessing myocardial perfusion are briefly characterized in the Table 20.1. These RPs have a common property of accumulating in cardiomyocytes proportionally to myocardial blood flow.

The main pharmaceuticals are cyclotron-produced (^{15}O -water, ^{13}N -ammonia) and generator-produced [^{62}Cu pyruvaldegide-2-4N-thyosemicarbasone (^{62}Cu -PTSM) and ^{82}Rb -chloride].

The pharmacodynamics of cyclotron-produced RP (^{15}O -water, ^{13}N -ammonia) is studied best of all. ^{15}O -Water belongs to metabolically inert RP; this is its main advantage over other perfusion agents labeled with positron-emitting radionuclides

(Bergmann et al. 1989). This RP freely penetrates through the cell membrane and is distributed in the myocardium in direct proportion to myocardial blood flow. An equilibrium is soon established between the ^{15}O -water concentration in cardiomyocytes and that in the vascular channel, which has a negative impact on the quality of visualizing the left-ventricular myocardium and correspondingly hinders the correct selection of the area of interest above the myocardium in calculating specific myocardial blood flow. In order to isolate the blood pool, an additional examination is done with carbon oxide labeled with ^{15}O . However, this makes the procedure more complex (Bergmann et al. 1989). For this reason the use of ^{15}O -water PET has not become widespread and it is applied mostly in experimental research.

^{13}N -Ammonia, in its turn, is widely used for assessing myocardial blood flow. Its half-life period is 9.96 min. When reaching the coronary channel, ^{13}N -ammonia is virtually entirely extracted by cardiomyocytes within 2–3 s. Its extraction fraction makes up 90–95% during the first passage of RP through heart capillaries. ^{13}N -Ammonia transport to cardiac cardiomyocytes occurs in two ways: by way of passive RP diffusion in the form of $^{13}\text{NH}_3$ solution and with participation of Na^+/K^+ -ATP-dependent pump in the form of $^{13}\text{NH}_4^+$. The balance between $^{13}\text{NH}_3$ and $^{13}\text{NH}_4^+$ is achieved within 19 ms after the RP arrives to the blood channel. ^{13}N -Ammonia extraction fraction at rest during the first passage of the bolus makes up approximately 90% (Gould 1999; Schelbert 2004). It should be noted that ^{13}N -ammonia extraction fraction is determined by two components: the intracellular transport rate and reverse RP diffusion from cardiomyocytes. ^{13}N -Ammonia intracellular transport rate is a relatively constant value, whereas reverse diffusion depends on the blood flow rate; the higher the blood flow rate, the bigger is reverse diffusion. According to experimental research data, when volume blood flow values range from 0 to 300 mL/100 g/min, ^{13}N -ammonia uptake by cardiomyocytes is directly proportional to myocardial blood flow. If the myocardial blood flow rate is above 300 mL/100 g/min, the ^{13}N -ammonia extraction fraction decreases to 35% (Schelbert 2004). Additionally, the ^{13}N -ammonia extraction fraction significantly decreases in myocardial ischemia and in systemic acidosis. ^{13}N -Ammonia in cardiomyocytes reacts with glutamic acid or alpha-ketoglutarate under the influence of the enzyme glutamyl synthetase and is accumulated in the form of ^{13}N -glutamine compound. High ratios of myocardium/left-ventricular cavity and myocardium/lungs provide the optimum contrast and quality of the myocardium image. Nevertheless, in patients with long experience of smoking, high RP uptake in lungs is observed. Elevated ^{13}N -ammonia uptake by hepatocytes in some cases makes it difficult to interpret the image of the inferior left-ventricular wall since it is screened by the liver, especially in hypersthenic patients. Normal ^{13}N -ammonia distribution in the left-ventricular myocardium is inhomogeneous: its uptake is lowered in the anterior wall due to the specifics of uptake and redistribution of ammonia metabolites in the myocardial tissue (Schwaiger 1994). However, this defect usually disappears in the dynamic series of left-ventricular tomograms; this permits to distinguish a real perfusion defect from an artifact.

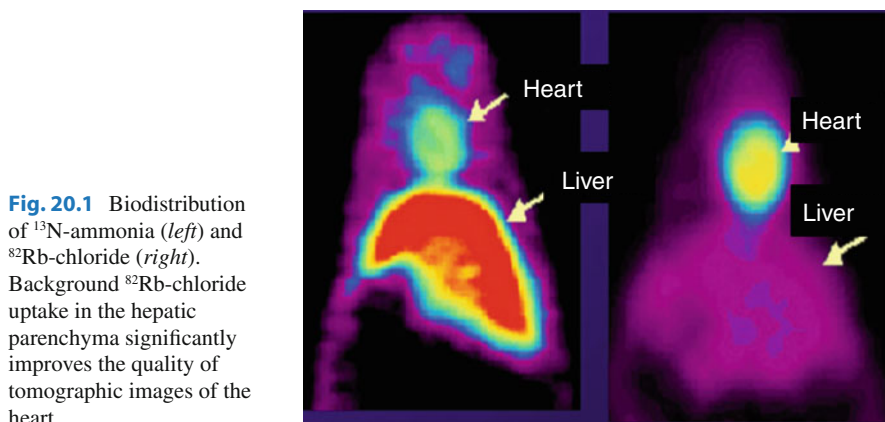
Ultra-short half-life periods of the isotopes ^{15}O and ^{13}N restrict the use of ^{15}O -water and ^{13}N -ammonia, since PET examinations are possible only in centers

equipped with a cyclotron and a radiochemical laboratory. For this reason much attention is attached to developing and introducing into clinical practice generator-produced positron emitting radionuclides, such as ^{82}Rb and ^{62}Cu .

^{62}Cu -Labeled 2–4N-thiosemicarbasone is used for assessing myocardial blood flow. This RP is a lipophilic compound of copper-62 and has some considerable shortcomings; the most significant of them are the following: non-linear extraction by cardiomyocytes that decreases with growth of the myocardial blood flow rate and high RP uptake by the liver, which causes diagnostical difficulties in interpreting the state of perfusion in the inferior wall of the left ventricle (Herrero et al. 1996; Wallhaus 1998). Therefore, this RP has not received wide clinical use.

^{82}Rb is a generator-produced isotope ($^{82}\text{Sr}/^{82}\text{Rb}$ generator with half-life period of 25.5 days) formed by way of the nuclear reaction of electron uptake. The half-life period of the ^{82}Rb isotope is 75 s. The ^{82}Rb isotope has served as the basis for developing the RP ^{82}Rb -chloride. The $^{82}\text{Rb}^+$ ion is an analog of the K^+ ion in its physical, chemical and biological properties and is used for assessing myocardial blood flow. The intensity of inclusion of ^{82}Rb -chloride in cardiomyocytes depends not only on the state of coronary perfusion, but also on the activity of the Na^+/K^+ -ATP-dependent pump and radionuclide transmembrane transfer rate. The main mechanism ensuring ^{82}Rb uptake in the myocardium is active transmembrane transfer with help of the Na^+/K^+ -ATP-dependent pump. During the first passage of the bolus through coronary vessels, some 50–60% of ^{82}Rb comes to cardiomyocytes (Gould 1999; Schelbert 2004). The extraction fraction decreases with growing blood flow rate down to 25–30%, as well as in ischemia and myocardial reperfusion due to suppression of the activity of the Na^+/K^+ -ATP-dependent pump and transmembrane transport.

^{82}Rb -chloride has some advantages, such as short half-life period of the ^{82}Rb isotope (76 s), enabling a shortening of the duration of patient examination and generator production, which does not require presence of the cyclotron in the PET center. Low RP uptake in the liver provides better-quality visualization of the inferior and anterior sections of the left-ventricular myocardium (Fig. 20.1). Besides advantages, ^{82}Rb -chloride has a number of shortcomings, such as low extraction fraction by



cardiomyocytes (50–60%). This requires injecting large doses of the RP. In their turn, PET scanners should be equipped with highly sensitive detectors which can perceive high ^{82}Rb -chloride doses (50–60 mCi) without the “dead time” being increased. For this reason, unlike other RPs used for assessing myocardial blood flow, ^{82}Rb -chloride cannot be used in studying myocardial perfusion with single photon emission scanners with high-energy collimators, crystals for registering photon energy at 511 keV and blocks registering signal coincidence. The high positron energy (3.15 MeV) of this radionuclide lowers the quality of the image and long positron path decreases spatial solution. The influence of the Na^+/K^+ -ATP-dependent pump on the ^{82}Rb -chloride uptake in cardiomyocytes can be considered in two ways. On the one hand, hypoxia occurring in transient ischemia decreases the activity of the Na^+/K^+ -ATP-dependent pump. Reduction in myocardial blood flow combined with low transmembrane transfer of the $^{82}\text{Rb}^+$ ion permits detection with more reliability the areas of myocardial ischemia. On the other hand, the suppression of the Na^+/K^+ -ATP-dependent pump may result from other pathologic states unconnected with impairment of the coronary channel (acidosis, virus infection, taking beta-blockers, etc.).

It should be noted that the extraction of the indicated RP does not have linear dependence on the myocardial blood flow rate. While ^{15}O -water freely penetrates through cell membranes and is distributed in the myocardium in direct proportion to myocardial blood flow, the extraction level of other RPs determines the blood flow rate through the capillary channel, the state of transport (for example, Na^+/K^+ -ATP-dependent pump) and enzymatic systems.

20.2.3 The Methods of Tomographic Study of Myocardial Perfusion

PET examination of the heart includes two obligatory stages: the transmission and emission scanning. The transmission scan is done for correcting radiation dispersion with help of $^{68}\text{Ga}/^{68}\text{Ge}$ calibration sources built into the tomography, with subsequent reconstruction of the attenuation file. This examination is done immediately before the emission scan. The emission tomography is performed without changing patient position in the bed or according to previous marking on the patient's body.

During the procedure, the patient lies on their back in the scanner bed with their arms raised and put behind the head (the optimum position) or lowered and stretched along the body (an admissible position). The patient is placed into the gantry so that the upper boundary of the field of vision is situated at the level of the second to third intercostal space and the lower one is at the level of the xiphoid process. Under these conditions the left ventricle is thoroughly situated within the scope of scanning. If the procedure is done with use of a PET/CT scanner, patient positioning is much simpler since the area of PET scan is set according to a topogram done by means of CT. If data acquisition is done in the dynamic regime, the emission scanning starts immediately after the intravenous injection of the RP. In case of static data acquisition, the emission scan should be started 1.5–3 min after the introduction of ^{13}N -ammonia and 90–130 s. after injecting ^{82}Rb -chloride. The interpretation of cardiac PET images collected in

the static regime is based on the semiquantitative analysis, which consists of calculating the spatial RP uptake relative to the maximum values as percentages. However, in some clinical cases, for example in balanced myocardial ischemia, the semiquantitative data processing can underestimate the severity of coronary insufficiency due to multivessel coronary atherosclerosis or diffuse atherosclerosis.

The possibility of dynamic tomography is an unquestionable advantage of PET over perfusion scintigraphy since it permits to calculate specific myocardial blood flow in all the left-ventricular segments, as well as to express the obtained results in absolute units (mL/g/min) and to assess the coronary flow reserve. In addition, it is possible to form a static image of the heart in summing the last frames of the dynamic series. So, data acquisition in the dynamic regime is most advisable.

^{13}N -Ammonia is known to reach the coronary channel and to be virtually thoroughly extracted by cardiomyocytes roughly 1.5–2 min after its intravenous introduction. This is why static scanning should be started exactly in this period. The duration of examination should not exceed 20 min, since after two half-life periods of the ^{13}N isotope the general scintillation count will be very low, which will result in poor-quality tomoscintigrams.

Given the ultra-short physical half-life period of the ^{82}Rb isotope, PET with ^{82}Rb -chloride has a number of methodological peculiarities. In order to avoid excessive radiation exposure, correct patient positioning relative to the field of vision of the tomography is necessary. For this purpose, before the examination a CT topogram (for PET/CT scanners) or scout scan for PET should be done. The diagnostic dose of ^{82}Rb -chloride depends on the technologic characteristics of the PE tomography, including the chemical composition of the detectors and 2D or 3D scanning regime. Without going into detail (this material has been expanded in the introductory chapter), we will only stress that in spite of high diagnostic doses, the radiation exposure of the patient from ^{82}Rb -chloride PET does not exceed that of traditional perfusion single photon emission tomography and ^{13}N -ammonia PET. This is due to the ultra-short half-life period of the isotope. However, radiation exposure to the personnel is much higher than in the case of other isotopes. Therefore, the procedure should be performed with use of remote control. After the ^{82}Rb -chloride injection, whose duration should not exceed 30 s, emission scanning in persons with left ventricular ejection fraction above 50% can be started after a lapse of 70–90 s, while in persons with left ventricular ejection fraction equal to 50% and less it should be started after 110–130 s. This difference in time is due to the slowdown of systemic hemodynamics in persons with cardiac insufficiency. It is necessary to correct an ^{82}Rb -chloride PET sonogram for the values of random scattering, dead-time period, absorption of photon energy and physical half-life period before the onset of the process of reconstruction.

20.2.4 The Methods of Stress Testing

According to most specialists in nuclear cardiology, perfusion PET of the heart at rest is relatively lowly informative. In atherosclerosis-induced lessening of the

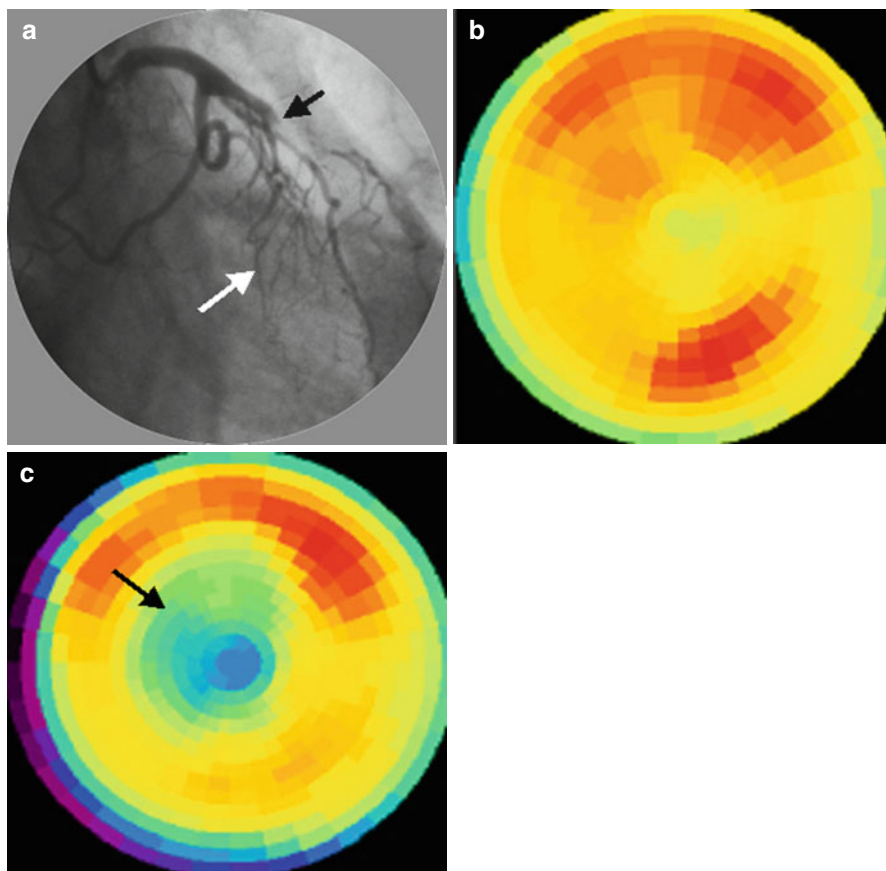


Fig. 20.2 Selective X-ray coronarography (a). The roentgenogram is done in the right oblique projection with cranial inclination of the tube. Occlusion of the proximal segment of the anterior interventricular branch of the left coronary artery (*black arrow*). Network of collateral vessels from the enveloping branch of the left coronary artery (*white arrow*). ^{13}N -Ammonia PET of the heart. Polar maps of the left ventricle. Perfusion defects are not detected when during examination at rest (b). Under exercise stress test (c) a reversible perfusion defect is visualized in the apical and medium segments of the anterior left-ventricular wall and anterior part of the interventricular septum (*arrow*)

coronary lumen, a compensatory vasodilation of the affected vessels takes place and besides that a net of collateral blood circulation is formed. For this reason, myocardial blood supply may remain virtually normal at rest, while a disorder in myocardial blood flow can be detected only under the conditions of a functional load (Fig. 20.2). Examination under stress testing does not permit the detection of a reduction in blood flow in myocardial segments nourished by arteries with stenoses no larger than 50% of the vascular cross-section, which confirms the justice of the term “hemodynamically insignificant stenoses,” referring to the narrowing of the vascular lumen below 50% of the cross-section.

The difference between myocardial blood flow under stress and at rest is called *coronary flow reserve*, which is an integrated index characterizing coronary hemodynamics at the level of large epicardial vessels and microcirculation channel. Stress testing includes an *exercise test* on a bicycle ergometer or a treadmill, *pharmacologic test* with vasodilators – dipyridamole, adenosine and A2-adenosine receptor agonists or with the β 1-adrenoreceptor agonist dobutamine, *transesophageal electrocardiostimulation* and *cold pressor test*. Transesophageal electrocardiostimulation has not received wide use in nuclear cardiology, since this procedure is not well tolerated by the patients and in addition requires more expensive equipment.

Before we proceed to the methodology of stress testing in nuclear cardiology, we have to dwell at length on the counterindications for it: it is the cardiologist who makes the decision on doing a radionuclide examination and is responsible for eventual complications consequent to the procedure. The absolute counterindications for stress testing are the following:

- Acute cardiac infarction
- Unstable stenocardia
- Cardiac insufficiency of a high functional class
- Presence of chronic aneurism with thrombus
- Acute disorder of cerebral blood circulation
- Hemodynamically significant aortic stenosis and subaortic stenosis
- Heart diseases in decompensation stage
- Acute thrombophlebitis
- Feverishness
- Marked respiratory failure

The relative counterindications include: marked arterial hypertension (arterial pressure > 180/100 mmHg), sinus tachycardia (pulse rate > 110 beats/min), marked disorders of rhythm and conduction, decompensated diabetes, hypothyroidism and thyrotoxicosis, and psychoneurologic disorders.

The most physiologic test is considered to be the one with exercise, during which there is an increase in myocardial oxygen demand due to increased heart rate, which is normally accompanied by higher myocardial blood flow. Many researchers prefer the treadmill test as simpler and more physiologic for the patient. Usually a higher frequency of heart contractions is obtained during the treadmill test than on a bicycle. Under the stress test, constant ECG control and monitoring of the arterial pressure are necessary at the end of every stage as well as during the rehabilitation period.

RP injection is done when the criteria for interrupting the exercise test are met, which are the following:

- A fit of stenocardia or its equivalent (asthmatic fit, atypical pain syndrome, etc.)
- Lowering of systolic arterial pressure in the maximum load by 10% and more compared with the initial level
- Dangerous disturbances of ventricular rhythm

- Symptoms of acute myocardial ischemia according to ECG data (horizontal depression of ST segment no less than 1 mm, obliquely descending or obliquely ascending displacement of ST segment making up 2 mm and more at the distance of 60 ms from the “j” point, rise of ST segment by 1 mm and more)
- Achieving the submaximum heart rate according to the age of the patient

After the RP injection the test continues for 60 s more. The emission scan is done in the static regime; it begins 1.5–2 min after the end of the test. The emission scan is followed by the transmission scan. Additional counterindications for the exercise test are traumas and diseases of the locomotive system, thrombophlebitis in remission stage, and vascular atherosclerosis of the lower limbs.

Pharmacologic tests with vasodilators (dipyridamole, adenosine and A₂-adenosine receptor agonists) are based on the adenosine hypothesis on vascular tone regulation, which has been mentioned above. One of the most widespread pharmacologic tests with vasodilators is the one with dipyridamole. The action mechanism of dipyridamole consists of blocking the enzyme adenosinedezaminase and consequent adenosine uptake; adenosine when reacting with A₂-adenosine receptors of cell membranes of the arteriolar smooth musculature induces an increase in the intracellular level of cyclic adenosinemonophosphate and vascular dilatation. The myocardial ischemia is due to the phenomenon of “intercoronary steal”. As a consequence of blood flow redistribution, a decrease in perfusion pressure occurs below the site of coronary obstruction, which results in reduction in myocardial blood supply, especially in the subendocardial sections, as well as in lowered blood flow through capillaries. In doing the test the injection form of dipyridamole should be used. The pharmaceutical is introduced intravenously at a dose of 0.56 mg/kg, normally over 4 min. The injection should be done on the 6th min from the start of dipyridamole infusion (the maximum vasodilating effect is reached precisely by 6–7 min from the beginning of the test) or at the moment of the typical angina, arrhythmia and ischemic changes in the ECG. Dynamic data acquisition begins immediately after the injection of RP. The transmission scan should be done before the pharmacological test starts.

In roughly one-third of patients the following side effects of the RP are observed due to systemic vasodilatation. An intravenous injection of the specific adenosine agonist aminophylline will completely remove these side effects.

The main advantage of adenosine as a pharmacological stress agent is its rapid metabolism in blood plasma (10 s). During the loading test adenosine infusion at a dose of 140 mL/kg/min is done for 6 min, immediately followed by RP injection and the start of dynamic emission scanning. The growth of myocardial blood flow due to the pharmacological test depends also on the medicinal substance serving as vasodilator: in case of infusion of the standard adenosine dose, myocardial blood flow values are higher than in the case of injecting dipyridamole (Chareonthaitawee et al. 2001). Side effects develop more frequently in the adenosine test than in the dipyridamole test, but they are transitory and pass on their own after the infusion is over. The specific counterindications for tests with use of vasodilators are: atrioventricular heart block of degrees I and II, sick sinus syndrome, long QT syndrome, chronic obstructive lung diseases, high intracranial pressure, hypovolemia, presence of curantyl in the patient’s basic therapy.

The pharmacological test with the β ₁-adrenoreceptor agonist dobutamine is based on the elevated myocardial oxygen demand due to a dobutamine-induced

increase in arterial pressure and cardiac rhythm. In principle, the pharmacological test with dobutamine is a reliable alternative to the exercise load test. Besides the increased myocardial oxygen demand, an important role in the development of ischemia belongs to elevated myocardial tension due to the lessened share of diastole in the cardiac cycle and lowered perfusion pressure more distal relative to stenosis, caused by accelerated coronary blood flow.

Transmission scanning is done before the start of the pharmacological test with dobutamine. The initial RP perfusion rate is 5 $\mu\text{g/kg/min}$, the rate of injection is increased every 3 min by 5 $\mu\text{g/kg/min}$ up to 40 $\mu\text{g/kg/min}$. The RP injection is done at the end of the last stage of the test or at the moment of emergence of the typical anginous fit or stenocardia equivalents, rhythm disturbances and ischemic changes in the ECG. Dynamic data acquisition should be started immediately after the injection of RP.

The side effects of the pharmaceutical consist in palpitation, disturbances of the cardiac rhythm, reddened face, anxious feeling, unpleasant sensations in the thorax and abdomen. The mentioned phenomena disappear after the dobutamine infusion is stopped, however in some cases an intravenous injection of beta-adrenoceptor antagonists is needed.

The cold pressor test is physiologically based on the activation of the sympathetic autonomic nervous system, accompanied by an increase in myocardial oxygen demand. Reacting with α_2 -adrenoreceptors of endotheliocytes, catecholamines stimulate nitric oxide release, nitric oxide being the main endothelium-relaxing factor. Increased nitric oxide concentration on the surface of the vascular wall balances the vasoconstrictive effect of catecholamines on the α_1 -adrenoreceptors of subjacent smooth-muscle cells. In case of synthesis abnormality or nitric oxide release by endotheliocytes in response to catecholamine stimulation, coronary artery vasodilatation is absent or a paradoxical vasoconstriction is observed, which results in a disbalance between myocardial oxygen supply and myocardial need in oxygen and consequently in the development of ischemia. The cold pressor test is preceded by transmission scanning, then the patient's upper left or lower left limb is immersed in cold water (without them changing their position in the tomographic bed), and 45 s after the immersion the RP is injected to the right cubital vein. After the RP injection the test continues for 60 s. During the test the arterial pressure is measured twice; the test is accompanied by constant monitoring of ECG and heart rate. The emission scan is started immediately after the injection of RP.

If possible, PET examination at rest should precede the examination during the loading test in order to avoid residual effects of ischemia (stunning, steal syndrome). The time interval between ^{13}N -ammonia injections is about 100 min (10 half-life periods of ^{13}N), while for ^{82}Rb -chloride it is 12 min (10 half-life periods of ^{82}Rb).

20.2.5 Interpreting the Results of PET of the Heart

Cardiac PET scan provides a series of static or dynamic images of the left ventricle in the transaxial plane. The right ventricle is visualized only in some pathological states, for example in presence of high pulmonary hypertension; as for the two atrial walls, RP uptake in them is not observed even in case of their hypertrophy. In order

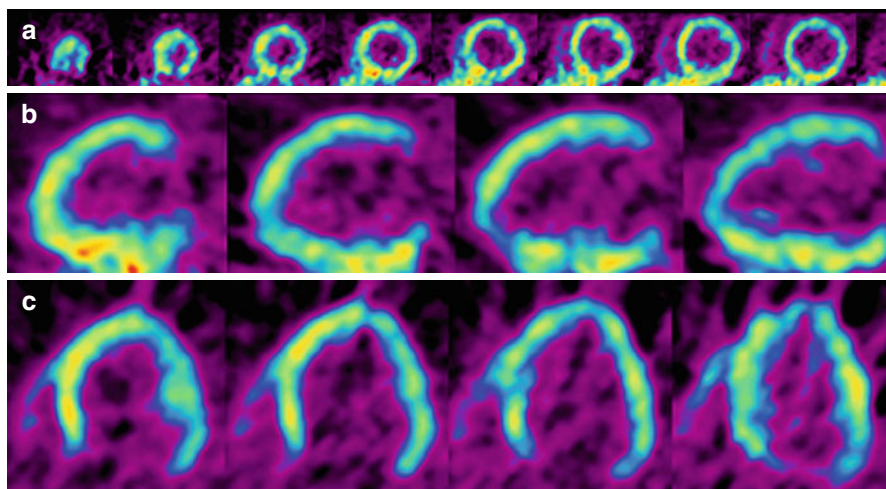


Fig. 20.3 Series of tomographic cuts of the left-ventricular myocardium along the short (a) and long axes: vertical cuts (b) and horizontal cuts (c). All the left-ventricular segments from the apex to basal segments are visualizable

to interpret PET results, it is necessary to form left-ventricular sections along the three standard anatomical axes: vertical and horizontal sections along the long axis and a series of sections along the short axis of the left ventricle (Fig. 20.3). These sections are done perpendicularly to the walls of the left ventricle.

Besides a series of tomographic sections of the left ventricle, linear or circular profiles are formed. The method of polar left-ventricular mapping is the widest spread; it consists of transforming a series of tomographic sections into an integral left-ventricular image (Fig. 20.4). The transformation is done automatically by means of the software package of the scanner.

Describing tomoscintigrams begins with visual assessment of the obtained sections, because of potential artifacts due to movements of the patient. The latter is detected in heart tomograms in patients after the exercise test. This occurs as a consequence of a gradual decrease in frequency of heart contractions and rarefaction of respiratory excursions of the thorax. The diaphragm then rises and displaces the heart upwards, which leads to lower-quality tomoscintigrams due to the vague contours of the image of the left-ventricular myocardium; sometimes this induces a “false-positive decrease” in RP uptake. In order to avoid this phenomenon, it is better to start the emission scan 4–5 min (and not 1.5 min) after the injection of RP. Heart displacement is not usually observed during pharmacological tests, with the exception of the dobutamine test. Owing to the correction of radiation dispersion and absorption due to transmission scanning, there are no artifacts induced by the myocardium being screened by the mammary gland and diaphragm. When heart perfusion is examined with use of ^{13}N -ammonia, RP uptake in hepatic tissue may induce an artifact occurring in image reconstruction and showing up as low RP

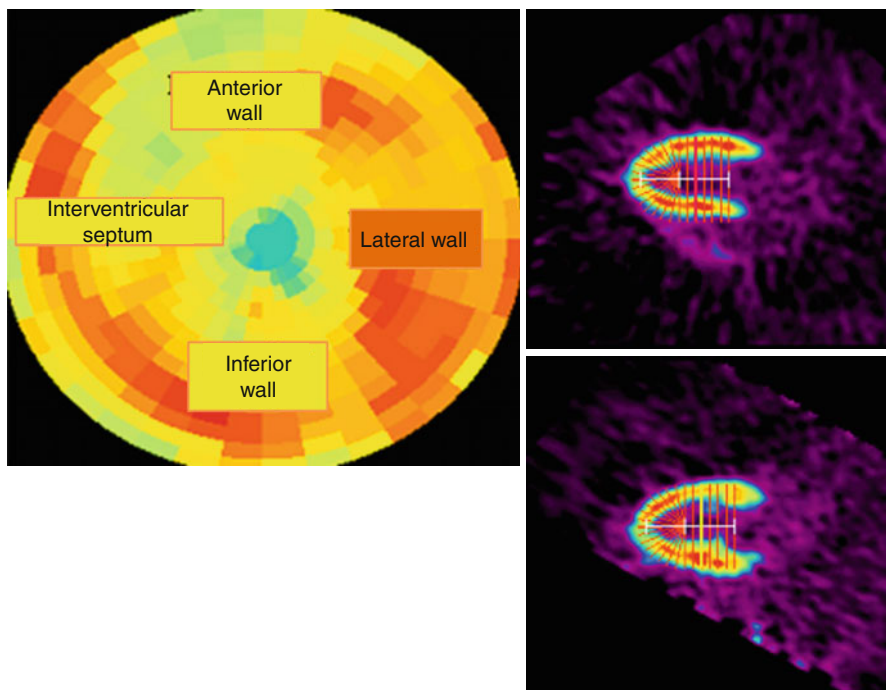


Fig. 20.4 Polar left-ventricular map. The cardiac apex is reflected in the center of the circle, basal cardiac segments are in the periphery. The upper sector of the circle represents the anterior left-ventricular wall, the right lateral sector stands for the lateral and posterior walls, the lower sector signifies the inferior wall and the left lateral sector represents the interventricular septum

uptake in the left-ventricular myocardium. In order to avoid such an artifact, the iterative algorithm of reconstruction should be used.

During the visual analysis of tomoscintigrams the homogeneity of perfusion agent uptake in the left-ventricular myocardium, the intensity of RP uptake by the right-ventricular myocardium and RP uptake in the pulmonary parenchyma are assessed. The left-ventricular tomographic image is characterized by even RP uptake in all the parts, excluding the apex and the basal segment of the interventricular septum. Low uptake of perfusion indicators in the basal segment of the anterior interventricular septum is caused by prevalence of fibrous tissue in this area. A similar situation is observed in doing perfusion scintigraphy. A decrease in ^{13}N -ammonia uptake in the basal segment of the posterior left-ventricular wall in persons without cardiovascular diseases was reported in other studies and was accounted for by the biochemical specifics of ^{13}N -ammonia metabolite redistribution in the myocardial tissue (Fig. 20.5).

The right ventricle is normally visualized at the background level. However, in patients with high pulmonary hypertension an elevated RP uptake is observed in the right ventricular myocardium, even in absence of its hypertrophy.

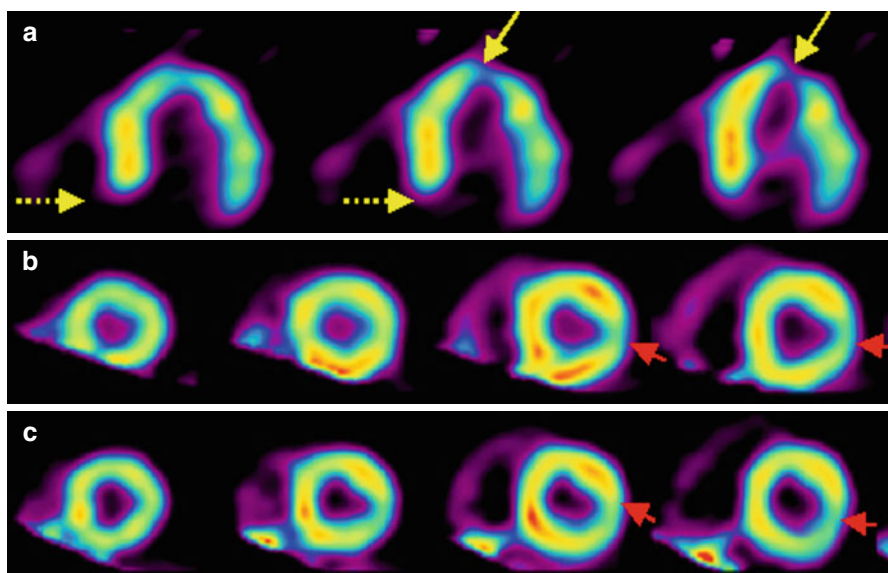


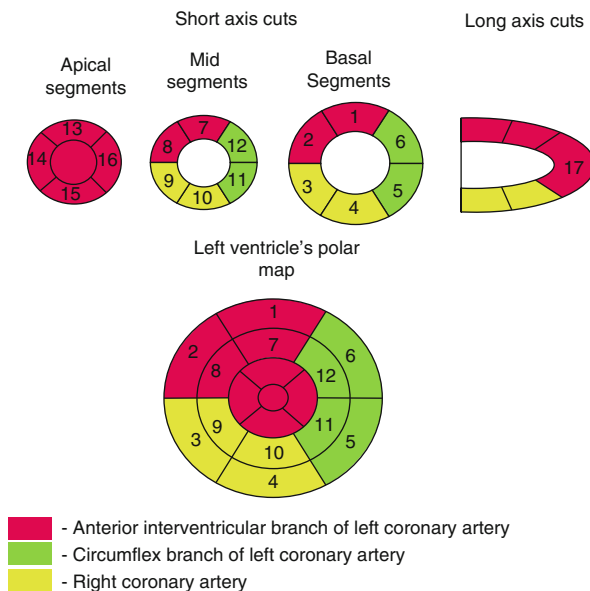
Fig. 20.5 ^{13}N -Ammonia PET in a patient without cardiovascular pathology. Horizontal left-ventricular cuts (a), series of cuts along the short axis at the level of the medium and basal segments at rest (b) and under dipyridole test (c). In the normal state a relative decrease in ^{13}N -ammonia uptake in the left-ventricular apex (yellow arrow), basal segment of the posterior wall (red arrow) and basal segment of the interventricular septum (yellow dotted-line arrow)

High ^{13}N -ammonia uptake in the pulmonary parenchyma is observed in congestive heart failure, chronic obstructive lung diseases and in people with long experience of smoking.

The degree of myocardial blood flow disorder is determined by the area and severity of perfusion defects relative to the conditionally unaffected myocardium. For this purpose, the PET results are compared with the data base of normal values. PET/CT scanners are usually equipped with special program packets for processing the results of perfusion examinations. Software packets include the database of normal values. An alternative approach to assessing the severity of perfusion defects is calculation of RP uptake by segments relative to the minimum values of RP uptake in the myocardium expressed as percentages. According to the recommendations of the American Association of nuclear cardiologists, the walls of the left ventricle are divided into 17 segments, the area of each segment approximating to 6% of the overall left-ventricular area (Fig. 20.6). Perfusion defects whose area is up to 10% of the left-ventricular area are considered as small, while those with area of 11–20% are regarded as medium and those with area above 20% as large. The area of a perfusion defect has much prognostic value and its size is one of the main factors in justifying indications for surgical treatment of ischemic heart disease (Hachamovitch et al. 1996).

The severity of perfusion defects determined by comparing the examination results with the database of normal values is assessed with a five-point scale: 0 – normal, 1 – doubtful hypoperfusion, 2 – moderate hypoperfusion, 3 – severe hypoperfusion and 4 – apertfusion. According to this system, the state of myocardial

Fig. 20.6 Scheme of the 17-segment left ventricular model. The 1st, 7th and 13th segments correspond to the anterior left-ventricular wall. The 2th and 8th segments correspond to the anterior interventricular septum. The 3th, 9th and 14th segments correspond to the posterior interventricular septum. The 4th, 10th and 15th segments correspond to the inferior left-ventricular wall. The 5th and 11th segments correspond to the posterior left-ventricular wall. The 6th, 12th and 16th segments correspond to the lateral left-ventricular septum. The 17th segment represents the left-ventricular apex



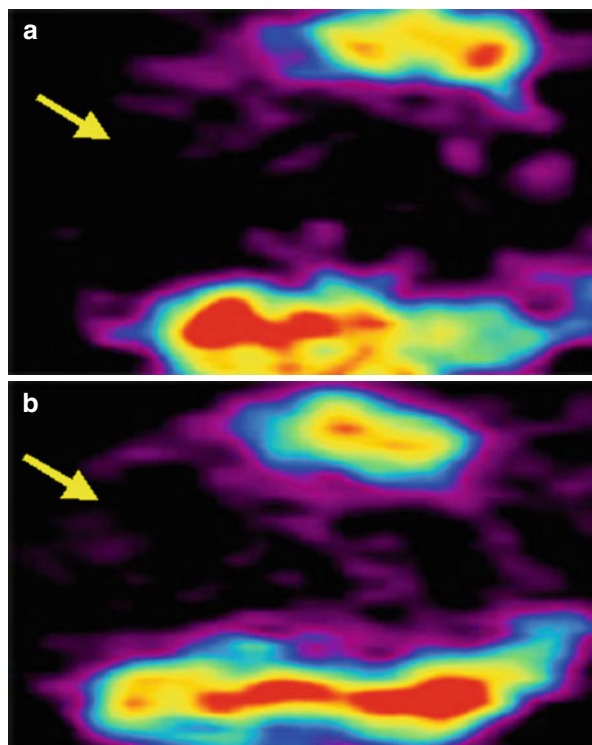
perfusion in each system is assessed at rest and at the loading test. Such an approach to assessing the results of perfusion PET has been called *semiquantitative analysis*.

The perfusion defect score is an integral PET indicator of the degree of severity and spread of coronary blood flow pathology. This score is calculated as the sum of points of all the left-ventricular segments. There are distinguished the score of perfusion defect at rest (Summed Rest Score), under stress test (Summed Stress Score) and the score of stress-induced perfusion defect (Summed Difference Score) being the difference between the two previous ones. The Summary Difference Score has much prognostic significance. If it is less than 4, the probability of unfavorable coronary occurrences is minimal (0.3% per year), while its values from 4 to 7 characterize a slight disturbance of myocardial blood flow and increase the probability of unfavorable occurrences. Summed Difference Score from 8 to 11 corresponds to medium severity of hypoperfusion; if it is more than 12, it indicates severe disturbances of myocardial perfusion and high risk of coronary complications (3.7% per year).

In order to detect the areas of stress-induced myocardial ischemia, examination results at rest and those under stress test are confronted by segments. Perfusion defects are considered as fixed if their area remains invariable during the loading test and the degree of perfusion disturbance grows or lessens by less than 1 point compared with the initial state (Fig. 20.7). Partially reversible perfusion defects are characterized by the presence of hypoperfusion at rest whose degree aggravates during the loading test by 1 point or more (Fig. 20.8). Reversible defect manifests itself with hypoperfusion only during the loading test (Fig. 20.9).

Dynamic tomographic examination permits the calculation of the specific myocardial blood flow in all the sections of the left ventricle and expression of the obtained results in absolute units (mL/100 g/min), which is an important advantage of PET over perfusion scintigraphy of the myocardium.

Fig. 20.7 Stable perfusion defect. ^{13}N -Ammonia PET of the heart. Vertical left-ventricular cuts. At the examination at rest (a) a zone of marked hypoperfusion is visualized in the left-ventricular apex and anterior wall; its area and degree do not change under pharmacological test (b) (arrow)

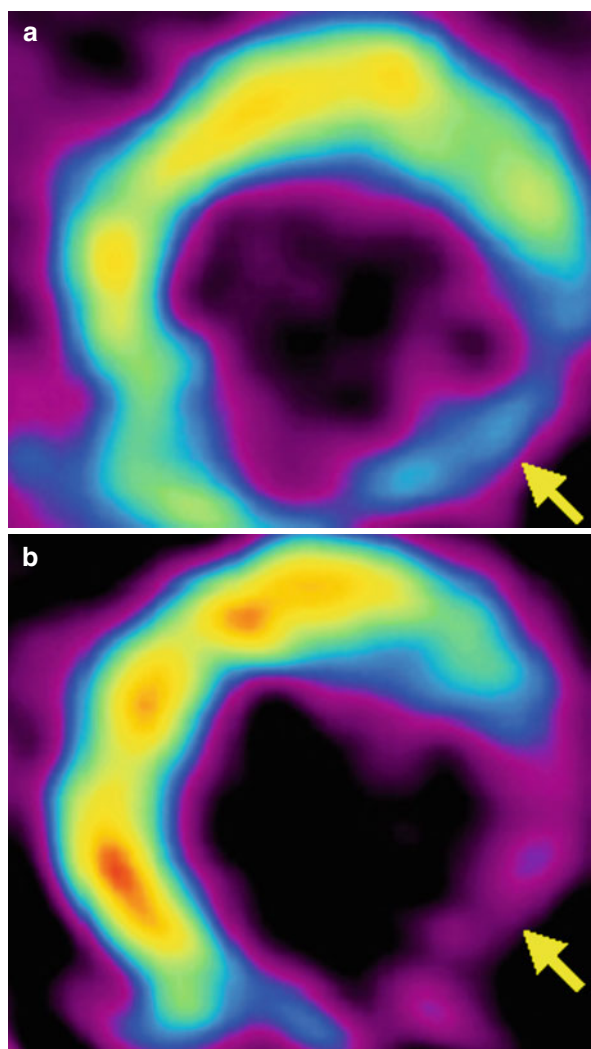


The one-compartment model for describing the pharmacokinetics of water has been created on the basis of Kety's mathematical developments (Kety 1951). In order to describe the transport of ^{13}N -ammonia and ^{82}Rb -chloride to cardiomyocytes, the two- or three-compartment models are used (Choi et al. 1999; Gould 1999). In the end it is always necessary to correct the obtained values of myocardial blood flow for the coefficient of residual RP volume in the left-ventricular cavity (recovery coefficient), spillover effect and RP metabolites. All these indices have been obtained in experimental research for all the RPs. In order to more accurately calculate the recovery coefficient, it is necessary to know the thickness of the left-ventricular walls, which can be established with ECG (Schelbert 2004).

As indicated before, in order to calculate myocardial blood flow values it is necessary to determine the change in RP concentration in blood plasma in the course of time. For this purpose multiple intakes of arterial blood are done and specific RP activity is determined in the samples. This method is invasive since it requires paracentesis of the peripheric artery. Besides, the method is laborious and therefore rarely used in clinical practice. Analogous information may be obtained by constructing time/activity curves above the area of the ascending aorta, left-atrial cavity or left ventricle with use of a dynamic series of PET images. This makes the procedure much simpler. The semiquantitative processing of PET results with perfusion RPs is the widest spread in clinical practice.

Fig. 20.8 Partially reversible perfusion defect.

^{13}N -Ammonia PET of the heart. Left-ventricular cuts along the short axis. During examination at rest (**a**) a marked hypoperfusion area is visualized in the posterior left-ventricular wall. Under pharmacological test (**b**) an increase in area and aggravation of severity of the initial perfusion defect are observed (*arrow*)

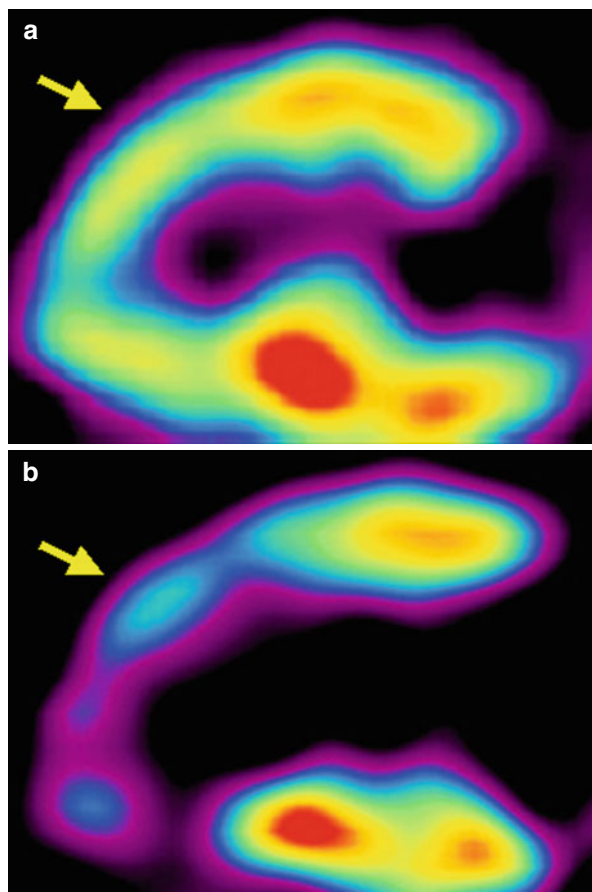


20.3 Technical and Methodological Aspects of PET in Assessing Myocardial Metabolism

20.3.1 Cardiovascular Energy Metabolism in Normal and in Pathological States

The term “metabolism” designates the whole of physical and chemical transformations occurring in a living organism; that is the processes of anabolism and catabolism. In virtue of these processes, various substances are taken in by the organism from the environment, assimilated and used in vital functions either as

Fig. 20.9 Reversible perfusion defect. ^{13}N -Ammonia PET of the heart. Vertical left-ventricular cuts. During examination at rest (**a**) no significant regional perfusion defects are detected. (**b**) Under pharmacological test with dipyridamole a perfusion defect is detected in the left-ventricular apex and anterior wall (arrow)



material for constructing cellular and tissue structures or as energy sources. The final stage of metabolism is excretion to the environment of end products of biochemical reactions. Anabolic processes are essentially intracellular biosynthesis of complex organic molecules, while catabolic reactions are aimed at providing the cell with the necessary reserve of biological sources of energy, phosphocreatine and ATP.

In the whole course of human life, the cardiac muscle incessantly performs electrical, mechanical and biochemical functions; in order to preserve them in cardiomyocytes, energy should be produced continuously and in sufficient amounts. The metabolic sources of biological synthesis of ATP are glucose, long-chain fatty acids (oleic, palmitic and stearic), amino acids, ketone bodies and lactic acid. In the presence of a sufficient amount of oxygen, 60–80% of the ATP is formed due to the oxidation of long-chain free fatty acid oxidation. Independently of the initial energy substrate, the final product of catabolic cascade is acetyl-coenzyme A (acetyl-CoA), which in turn undergoes metabolic degradation in the tricarboxylic acid cycle

(Krebs cycle) with formation of molecules of reduced nicotinamide adenine dinucleotide (NADN) and flavine adenine dinucleotide (FADN). Further oxidation of NADN and FADN is done by enzymes of the respiratory chain in mitochondria and is associated with the oxidative phosphorylation process: that is ATP formation due to etherification of mineral phosphate. ATP moves from the mitochondria to cytosol with the help of the carrier protein adenine nucleotide translocase and is used in various metabolic reactions.

Long-chain free fatty acid (FFA) transport from blood plasma to cardiomyocytes is a complex multistage process, including FFA transfer through the outer membrane of endotheliocytes, passage through their cytoplasm and intercellular space. Reaching the outer membrane of cardiomyocytes, FFAs pass through it and into the cytoplasm and into mitochondria as their final destination. It was initially supposed that FFA transfer through membranes occurs by way of passive diffusion. Then the theory of passive transmembrane transport as the only transfer mechanism of long-chain FFAs was revised. Kinetic research has shown that long-chain FFA transfer is ensured by specific transport proteins. Proteins transporting long-chain FFAs are divided into two groups: proteins integrated into cell membranes and intracellular carrier proteins (Schwenk et al. 2008). The first group includes *albumin-binding protein* situated in the membrane of the endothelium and of different parenchymatous organs, *fat acid binding protein of the plasma membrane* (FABPpm) situated on the exterior surface of the cell membranes of endotheliocytes and cardiomyocytes (it promotes membrane absorption of fatty acids), fatty acid transporting protein (FATP) and fatty acid translocase (FAT/CD36), which are integrated in the membranes of the endothelium and myocytes. The class of intracellular carrier proteins includes the epidermal type of fatty acid binding protein abundant in the endothelial cytoplasm, heart fatty acid binding protein (H-FABP) contained in the cytoplasm of cardiomyocytes and endothelium, and protein binding acetyl coenzyme A in the cytoplasm of cardiomyocytes.

Due to the variability of the structure of the superficial domain, it is accepted to distinguish five isoforms of the fatty acid transporting protein. The domain transformed to the cytosol has an analogous structure for all the isoforms of FATP. Fatty acid translocase FAT/CD36 has high affinity with long chain FFAs and performs their transmembrane transfer. The properties of FABPpm have been studied best of all. In 1985, Stremmelet and coworkers first discovered this protein with a molecular weight 40–43 kDa in the cell membrane of hepatocytes and demonstrated its high affinity with FFA (Stremmel et al. 1985). It has been established that the amino acid sequence of this protein is analogous to mitochondrial aspartate-aminotransferase (Stump et al. 1993). When FABPpm binds with specific antibodies, there occurs an inhibition of FFA inclusion by adipocytes, hepatocytes and histiocytes (Sorrentino and Potter 1988). In the presence of FATP gene expression there is an increase in intracellular long-chain FFA transport (Isola et al. 1995).

The delivery of long-chain FFA to the site of their oxidation (to mitochondria) occurs with participation of the H-FABP within the cytoplasm of the cardiac histiocyte; carnitine performs transmembrane transport of FFA from the cytoplasm to mitochondria.

The first stage of beta-oxidation is FFA activation. FFA is metabolically inert no matter how long the hydrocarbon chain and it cannot undergo any biochemical transformations including oxidation until it is activated. FFA activation occurs on the exterior surface of the mitochondrial membrane with participation of ATP, coenzyme A and Mg^{2+} ions. The reaction is catalyzed by the enzyme acyl-CoA-synthetase. The reaction forms the acyl-CoA-activated coenzyme form of FFA.

Coenzyme fatty acid (CFA) is not able to penetrate inside mitochondria where beta-oxidation occurs. Carnitine serves as the long-chain CFA transporter through the interior mitochondrial membrane. In consequence of the chemical bond between CFA and carnitine, acylcarnitine is formed which diffuses through the interior mitochondrial membrane. Fatty acid degradation occurs in the mitochondrial matrix by way of an oxidation reaction cycle, in which hydrocarbonic links segregate in sequence in the form of acetyl-CoA (activated acetic acid). Sequential segregation of acetyl groups begins with the carboxyl end of CFA every time between carbonic atoms in the α - and β -positions. This is why the degradation reaction cycle is called beta-oxidation. Acyl-CoA in mitochondria first of all undergoes enzymatic dehydrogenation by acyl-CoA-dehydrogenase with the formation of unsaturated acyl-CoA (enoyl-CoA). Enoyl-CoA binds with the water molecule with participation of the enzyme enoyl-CoA-hydratase and β -oxyacyl-CoA is formed. Then β -oxyacyl-CoA dehydration follows; the final stage of the metabolic cascade is a thiolase reaction, the crucial reaction of beta-oxidation, which is catalyzed by 3-ketoacyl-CoA-thiolase (β -ketothiolase). As a result, a detachment of acetyl-coA in the β -position occurs and also formed is a species shortened by two carbon atoms, acyl-CoA. The acetyl-CoA generated is the initial substrate of the tricarbo-xylic acid cycle.

In every beta-oxidation cycle, one FADN molecule and one NADN molecule are formed. In the process of their oxidation in the respiratory chain and the associated oxidative phosphorylation, two ATP molecules are formed from FADN and three ATP molecules are formed from NADN.

Altogether, five ATP molecules are formed in one beta-oxidation cycle. The cycle should repeat many times for complete degradation of the long-chain FFA. In the oxidation process of palmitic acid ($C_{15}H_{31}-COOH$), the cycle repeats seven times with the formation of 35 ATP molecules. In the beta-oxidation process of palmitic acid eight molecules of acetyl-CoA are formed, the decay of each of them in the tricarbo-xylic acid cycle leading to formation of 12 ATP molecules; the oxidation of eight acetyl-CoA molecules results in the production of 96 ATP molecules. Thus, the complete metabolic degradation of one molecule of palmitic acid results in formation of 131 ATP molecules.

Given that one ATP molecule is used in the formation of the active form of palmitic acid (palmitoyl-CoA), the total energy output in complete oxidation of one palmitic acid molecule is 130 ATP molecules. The contribution of FFA to energy metabolism lessens in the presence of exercise load, hyperglycemia or hyperinsulinemia, as well as when smoking and in a stress situation (Vander Vusse et al. 1992).

Glucose metabolism is also an important source of cell energy. Transmembrane glucose transport occurs with the help of the glucose-transporting protein GLUT. So far five isoforms of this protein have been identified which have different degrees of affinity to glucose. GLUT1 and GLUT3 have high affinity to glucose, therefore they ensure transmembrane glucose transport in its normal blood concentration. Usually the amount of such carrier-proteins is more significant in insulin-nonsensitive tissues. The glucose-transporting protein GLUT4 is observed in insulin-sensitive tissues such as fatty tissue, skeletal musculature and myocardium. GLUT4 is located in the cytoplasm of cardiomyocytes; the protein starts functioning as a glucose-carrier only after the entry of signal from receptor to insulin by means of the signal proteins phosphatidyl-inositol-3-kinase (PI3K) and atypical protein kinase C. The emergence of signal induces movement of GLUT4 to cell membrane.

The process of glucose catabolism is divided into two main stages: glycolysis and glucose oxidation. Glycolysis occurs under anaerobic conditions since it does not require presence of oxygen. The first key reaction of glycolytic cascade is glucose phosphorylation under the influence of the enzyme hexokinase and its transformation into glucose-6-phosphate. In the presence of sufficient oxygen supply, no more than 5–10% of ATP is formed in glycolysis. This way is considered to play an important part in maintaining the ion balance inside the cardiac histiocyte. Pyruvate, which is the end product of glycolysis, enters under normoxia conditions into the oxidative decarboxylation reaction chain and Krebs cycle with formation of the final products of energy metabolism: carbon dioxide and water; in the presence of hypoxia, pyruvic acid transforms into lactic acid. This reaction (of transformation of pyruvate into lactic acid) is reversible and does not require participation of oxygen molecules. In the process of glycolysis, four ATP molecules are formed from one glucose molecule, but two of them are consumed during the formation of glucose-6-phosphate and pyruvate. Thus, the anaerobic decay of glucose provides the energy potential of the cell with two ATP molecules. The glucose oxidation process continues and pyruvic acid arrives to mitochondria where it is transformed into acetyl-CoA during its oxidative decarboxylation with participation of the enzyme pyruvate dehydrogenase. Acetyl-CoA enters into Krebs cycle, where it is oxydated to CO_2 with participation of oxygen and 30 ATP molecules are formed in the process. In the issue, oxidation of one glucose molecule is accompanied by the formation of 32 ATP molecules, which is four times fewer than in oxidation of one molecule of palmitic acid. However, FFA metabolism requires high oxygenation of organs and tissues since the amount of oxygen consumed exceeds by 10–15% of that utilized in glucose metabolism to form the same quantity of ATP (Berezov and Korovkin 1998).

Energy formed in the course of aerobic metabolism is consumed for mechanical work of cardiomyocytes (Weiss and Hildbrand 1985; Ferrari 1996; Telkova and Teplyakov 2005). The reserve of ATP synthesized in aerobic glycolysis is enough to maintain cell homeostasis, support transmembrane potential, intracellular organelle reproduction and enzyme biosynthesis (Weissler et al. 1968; Nellis et al. 1991; Ferrari 1996).

Regulation of energy metabolism with participation of glucose and FFA occurs already when these energy substances enter the cardiomyocyte. Transmembrane transport of long-chain FFAs is inhibited by high glucose concentration; on the other hand, FFAs hinder the activation of protein kinase C and consequently suppress the insulin signal and disturb the function of GLUT4. Increase of NADH and acetyl-CoA in the cell due to FFA beta-oxidation results in suppression of the activity of pyruvate dehydrogenase (Garland et al. 1964). In addition, a high concentration of citrate inhibits the glycolytic activity of phosphofructokinase. The inhibition of phosphofructokinase induces an increase in concentration of glucose-6-phosphate, which in turn suppresses the activity of hexokinase. This leads to a slowdown of glycolysis, so that fatty acid oxidation becomes the main energy source.

High level of FFA in blood plasma and its intensified inflow to cardiomyocytes are observed in patients suffering from obesity, metabolic syndrome and diabetes because of low insulin content in the blood or lowered adipocyte sensitivity to it. This is why marked disorders of myocardial energy metabolism are observed in this patient category. Increase in FFA concentration in blood plasma with subsequent decrease in glucose uptake and utilization by skeletal muscles and myocardium occur also under fasting conditions.

20.3.1.1 Energy Metabolism in Ischemic Heart Disease

In presence of ischemia all the aerobic biochemical processes are disturbed: FFA beta-oxidation, oxidative decarboxylation, oxidative phosphorylation. Glycolysis becomes the main ATP source for the cell; its activation is a compensatory reaction. Under these conditions glycogen reserves are mobilized to support glycolysis (Opie and King 1998; Stanley 1997a, b) (Fig. 20.10).

In the presence of severe ischemia due to coronary artery occlusion, the anaerobic glycolysis remains the only source of ATP. This leads to excessive formation of pyruvic acid. The decrease in activity of the enzymes of the oxidative decarboxylation reaction chain induces the transformation of pyruvic acid into lactic acid and, in consequence, disturbance of the ion balance and intracellular acidosis, which in turn inhibits the activity of the key glycolysis enzyme, phosphofructokinase. In the presence of ischemia, FFA beta-oxidation in cardiomyocytes significantly decreases. Due to the inhibited function of carnitine palmitoyltransferase-1, the shuttle mechanism of acyl-CoA transport to mitochondria is disturbed. This leads to an increase in FFA concentration in the cytoplasm of cardiomyocytes, disturbed functioning of pyruvate dehydrogenase complex and a damaging effect of suboxidized products of FFA degradation on cell membranes. Increase in intracellular ATP content entails the inhibition of energy-dependent processes and, as a consequence, a rise in intracellular calcium concentration and decrease in contractile function of cardiac muscle. Adenosine diphosphoric acid is dissociated to adenosine, which reacts with adenosine receptors of sympathetic afferent nervous endings and provokes an anginous fit. Acidosis induces the opening of membrane potassium canals and issue of potassium from the cell. These processes receive irreversible character and entail the death of the cell in case of long hypoxia, when ATP concentration lowers down to the critical level (Hearse 1998). The sequence of pathological changes in

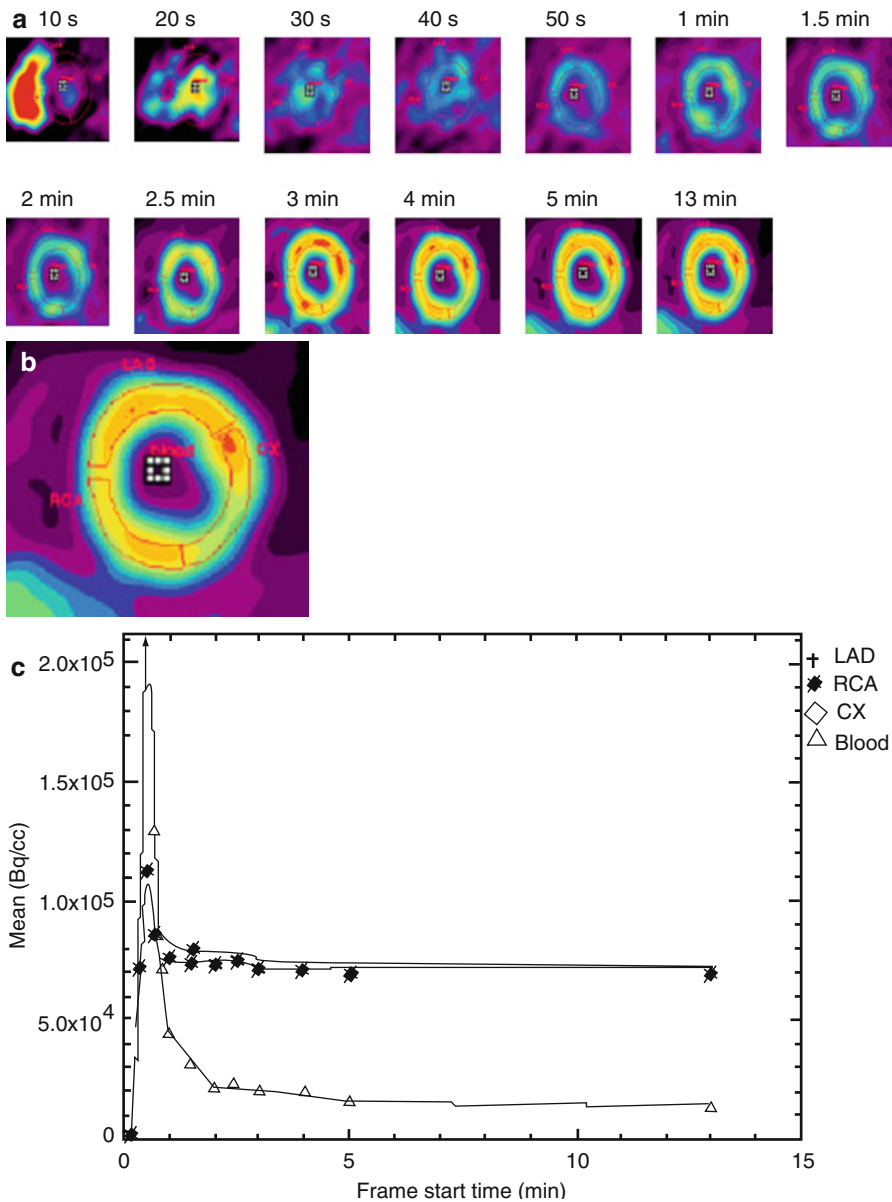


Fig. 20.10 A dynamic series of a left-ventricular myocardial cuts done along the short axis, the regions of interest are marked in the left-ventricular cavity and myocardium (a). A myocardial cut along the short left-ventricular axis (b). The areas of interest are marked in the left-ventricular cavity and myocardium according to the basins of the main coronary arterial branches: left anterior descending artery (LAD), circumflex artery (Cx), and right coronary artery (RCA). The activity-time graphs corresponding to the regions of interest in the left-ventricular cavity (blood) and left-ventricular myocardium (LAD, Cx, RCA) (c). The graphs demonstrate the change in ¹³N-ammonia concentration in blood plasma and in the left-ventricular myocardium with the course of time

metabolism, disturbances of functional and electrophysiological character induced by myocardial blood flow deficiency has been called “ischemic cascade,” pain syndrome being the final stage of the “ischemic cascade.”

Glucose metabolism in ischemic areas of the myocardium depends on a number of conditions; namely, on the state of the microcirculation channel, permeability of the capillary endothelium, functional activity of cell membranes and on the control factor (concentration of insulin, catecholamines, hormones in the thyroid gland, somatostatin, nitric oxide and bradykinin). Numerous studies have demonstrated the extremely high role of insulin in regulating vascular tone at the microcirculation level, in influencing the process of oxidative phosphorylation, enzyme biosynthesis, and transport and signal proteins (Cortight and Dohm 1997; Serne et al. 1999; McNulty 2000; Clarc et al. 2003; Sundell and Knuuti 2003).

Myocardial reperfusion after long-term ischemia is not always able to ensure adequate recovery of aerobic metabolism and cardiac function. In restoring coronary blood flow, FFA beta-oxidation process grows swiftly due to restored inflow of oxidated blood to previously ischemic foci of the cardiac muscle; the glucose oxidation process paradoxically decreases, since the excessive amount of FFA inhibits pyruvate dehydrogenase (Lopaschuk et al. 1994). The inhibition of glucose oxidation in mitochondria entails intensification of acidosis and growing damage to ischemic cardiac cells. The disbalance between glucose and FFA oxidation in favor of the latter, as well as elevated FFA concentration in the ischemic area, are the main factors of reperfusion injury: myocardial dysfunction and life-threatening rhythm disorders (Lopaschuk et al. 1993; Oliver and Opie 1994; Stanley 1997a, b; Wysocki 2004).

20.3.1.2 Energy Metabolism in Myocardial Hypertrophy

In case of pathologic myocardial hypertrophy, the suppression of FFA oxidation and an increase in glucose metabolism are observed (Allard 2004). Experimental research has provided results accounting for such changes in energy metabolism; they proved to be due to the shortage of FFA carrier proteins: the fatty acid binding protein (H-FABP) and fatty acid translocase FAT/CD36 (Zhang et al. 1995; Rosenblatt-Velin et al. 2001; Young et al. 2001). Experimental research has also demonstrated the absence of any limitations of mitochondrial FFA oxidation (Bache et al. 1999; Degens et al. 2003).

Unexpected information has been obtained concerning the regulation of transmembrane glucose transfer in myocardial hypertrophy. In homozygous mice, the genetically determined absence of GLUT4 was conducive to the development of myocardial hypertrophy (Katz et al. 1995). Complete absence of the glucose-transporting protein GLUT4 induced a compensatory increase in GLUT1. Expression of GLUT1 has a cardioprotective impact in the presence of pressure overload due to higher oxygen efficiency of glucose compared with FFA (Liao et al. 2002). The contractile function of the heart largely depends on the state of GLUT4-mediated glucose transport. Deficiency in GLUT4 causes a compensatory increase in activity of GLUT1 and a decrease in expression of proteins transporting FFA. This adaptive mechanism prevents the development of diabetic cardiomyopathy but has no

effect on cardiac function recovery. Thus, the glucose-transporting protein GLUT4 plays an important role in the regulation of energy metabolism.

20.3.1.3 Energy Metabolism in Diabetes

Energy metabolism disorders in diabetes are due to prevalent oxidation of fatty acids and suppressed glucose metabolism. Low concentration of insulin or cellular insulin resistance excludes the inhibiting effect of insulin on lipolysis in fatty tissue; this entails an increase in FFA concentration in blood plasma. High FFA level suppresses glucose extraction by cardiomyocytes and glucose oxidation. FFA transport in diabetes is significantly elevated due to the high activity of fatty acid translocase FAT/CD36. No irregularities are observed as far as beta-oxidation and tricarboxylic acid cycles are concerned; normal or slightly elevated activity of enzymes of the metabolic cascade is reported. This entails an excessive uptake of the end product acetyl-CoA in mitochondria and the inhibition of pyruvate dehydrogenase. Simultaneously with the inhibition of pyruvate dehydrogenase activity, the aerobic and anaerobic carbohydrate metabolism rate decreases sharply in the presence of diabetes. FFA oxidation is accompanied by an increase in intracellular concentration of citric acid, which in turn has a negative impact on the activity of phosphofructokinase – the key enzyme of glycolysis. It has been experimentally proved that transmembrane glucose transport is disturbed due to the low concentration of the glucose-transporting proteins GLUT1 and GLUT4 (Camps et al. 1992; Stanley et al. 1994; Hall et al. 1995). Depression of glycolysis manifests itself with excessive intracellular uptake of glucose-6-phosphate and decrease in the ratio of fructose-1,6-diphosphate/fructose-6-phosphate (Chen et al. 1984).

Suppression of glycolysis entails constant excess of calcium inside the cell. The uptake of calcium provokes dangerous consequences: disturbance in diastolic compliance, ATP deficiency and activation of phospholipases. Coronary insufficiency occurring in consequence of disturbed diastolic compliance can entail an irreversible impairment of the cardiac muscle. One of the defense mechanisms impeding calcium uptake in the cytoplasm consists of mitochondrial uptake of excessive calcium ions. Active reverse proton transport occurs in response to the change of the intramitochondrial charge. This process requires additional consumption of ATP intended for maintaining the contractile function of cardiomyocytes. The activation of phospholipase induces the impairment of cell membranes. ATP produced by glycolysis is also intended for the normal functioning of myocardial adrenergic neurons.

In diabetes, the lipid biosynthesis from acetyl-CoA is suppressed. As a result, the concentration of acetyl-CoA in the cytoplasm grows, which induces an increase in the level of acetylcarnitine and a decrease in carnitine concentration. As a consequence, acyl-coA transport to mitochondria is disturbed. For this reason the share of acyl-CoA in the triglyceride pool increases. The intensified uptake of long-chain fatty acids and their metabolites in the cytoplasm induces the activation of this process. The disturbance of myocardial fatty acid metabolism induces a number of functional disorders in cardiac activity. When products of fatty acid oxidation accumulate, a decrease in general and regional contractile functions is observed, as well

as disturbance of diastolic compliance (Liedtke et al. 1978); besides, the refractory period of excited cardiomyocytes shortens, which triggers life-threatening rhythm disorders (Russell and Oliver 1979).

Biochemical processes are the key to understanding the normal and pathological cardiac physiology, since any disorder of the cardiomuscular contractile function is based on a metabolic disorder. Here we deliberately presented in detail all the stages of glucose and FFA transmembrane transport and enzymic oxidation, both in the normal state and in various pathological states. The knowledge of the regulation mechanisms of biochemical transformations as well as that of key enzymatic reactions not only helps to correctly interpret the results of PET with labeled substrates of cell metabolism (labeled fatty acids, ^{18}F -fluorodeoxyglucose, ^{11}C -acetate, etc.) but also makes it easier to correctly assess the efficiency of modern antiischemic therapy of cardiovascular diseases.

20.3.2 RPs for Assessing Myocardial Metabolism

Most RPs labeled with positron emitting radionuclides are known to be natural biological substances or their analogs. When radionuclide is included into the molecule, it does not change their biochemical properties. Thus, the dynamics of RP uptake and concentration in various organs and tissues reflects real biochemical processes.

In order to assess glucose metabolism in cardiomyocytes, a synthetic analog is used: ^{18}F -fluorodeoxyglucose (^{18}F -FDG). The intracellular transport of ^{18}F -FDG occurs by means of the insulin-dependent glucose-transporting protein GLUT4. ^{18}F -FDG in the cell enters into a phosphorylation reaction under the influence of the enzyme hexokinase. Thereby ^{18}F -FDG-6-phosphate is formed, which cannot participate in the further chain of glycolytic reactions due to its chemical structure. ^{18}F -FDG-6-phosphate has low membrane permeability, which induces its uptake in myocytes. The RP does not accumulate in the pulmonary parenchyma; its uptake in hepatic tissue is not marked, which provides a high ratio of myocardium/background and correspondingly good quality visualization of all the left-ventricular segments. The capacities of PET with ^{11}C -palmitic acid or non-etherified analogs of fatty acids labeled with ^{18}F for assessing FFA metabolism in the myocardium have been widely studied since the 1980s (Schon et al. 1982; Schelbert et al. 1983). The RP ^{11}C -palmitic acid is a labeled analog of the native monobasic saturated long-chain fatty acid $\text{CH}_3(\text{CH}_2)_{14}-^{11}\text{COOH}$, in which the isotopic label ^{11}C is situated in the carboxyl group. The pharmaceutical form of ^{11}C -palmitic acid includes a 6% albumin solution. Albumin is a very important carrier protein, ensuring FFA transport in the blood flow to their destination: the cells of skeletal musculature, cardiac muscle and adipocytes. The study of the myocardial kinetics of ^{11}C -palmitic acid in patients without cardiovascular pathology has shown that some 67% of the substance is extracted by myocytes at its first passage through cardiomuscular capillaries in case of a volume blood flow rate equal to 1 ml/g/min tissue (Schon et al. 1982).

Labeled fatty acid enters the cell according to transport mechanisms presented in detail earlier under the heading “Cardiomuscular energy metabolism in normal and pathological states”. In cardiomyocytes the RP becomes bound with coenzyme A.

During the examination on an empty stomach about 67% of labeled fatty acid enters mitochondria with the help of the carnitine mechanism; there it undergoes further enzymatic degradation in the course of beta-oxidation and the tricarmonic acid cycle, with final formation of $^{11}\text{CO}_2$. About 33% of the labeled fatty acid is accumulated in the store of triglycerides and phospholipids.

The time/activity curve in the myocardium reflects the uptake and excretion of ^{11}C -palmitic acid from the cardiac muscle. It is a biexponential function composed of the fast or early phase (the first 20–30 min after the RP injection) and the consecutive slow or late phase of RP excretion. The oxidative way of utilization corresponds to the early phase in the time/activity curve, while transformation into ester corresponds to the late phase. Usually the duration of PET scan rarely exceeds 30 min in clinical studies; therefore the early phase is of the most interest for calculating fatty acid utilization rate.

If PET examination is done in the presence of hyperinsulinemia, only one-third of the amount of labeled fatty acid undergoes beta-oxidation, and the rate of its oxidation slows down significantly. Two-thirds of the introduced volume of labeled fatty acids is accumulated in the cytosol of cardiomyocytes in the form of triglycerides and phospholipids.

Sodium ^{11}C -butyrate is a Russian RP on the basis of the salt of a native short-chain fatty acid (butyric acid). It is synthesized by the Grignard reaction from ^{11}C -labeled carbon dioxide (without adding a carrier) and specially prepared propyl magnesium bromide in absolute ether (Grignard’s reagent). Before the injection, human albumin is added to sodium ^{11}C -butyrate solution in a proportion of 1:1. Clinical trials of this RP done in the PET center of the RSCRST have convincingly demonstrated its safety and diagnostic applicability in cardiology as well as in oncology.

In 1987, Brown and coworkers suggested using a labeled tricarmonic acid, ^{11}C -acetate for assessing oxidative metabolism rate in the myocardium. ^{11}C -Acetate freely enters cardiomyocytes and its activated form, acetyl-coenzyme A, is the initial metabolic substrate for the mitochondrial Krebs cycle. The radioactive label ^{11}C is excreted from cardiomyocytes in the form of $^{11}\text{CO}_2$. The clearance of ^{11}C -acetate closely correlates with oxygen consumption by cardiac histiocytes (Sun et al. 1998; Schelbert 2004). This is why ^{11}C -acetate is the most efficient RP for assessing oxygen consumption by cardiomyocytes. The time/activity curve for ^{11}C -acetate is determined by a monoexponential function and the inclination of the graph reflects the oxidative metabolism rate.

Recently much attention has been attached to the use of 14(R,S)-[^{18}F]-fluor-6-thia-heptadecanoic acid, a synthetic analog of long-chain fatty acid labeled with ^{18}F (^{18}F -FTHA). Like a native long-chain fatty acid, ^{18}F -FTHA is transported to mitochondria and undergoes only one reaction of beta-oxidation cascade enzymatic dehydrogenation, after which the metabolic transformation of ^{18}F -FTHA ceases and the biochemically modified RP is fixed in cardiomyocytes. It has been experimentally

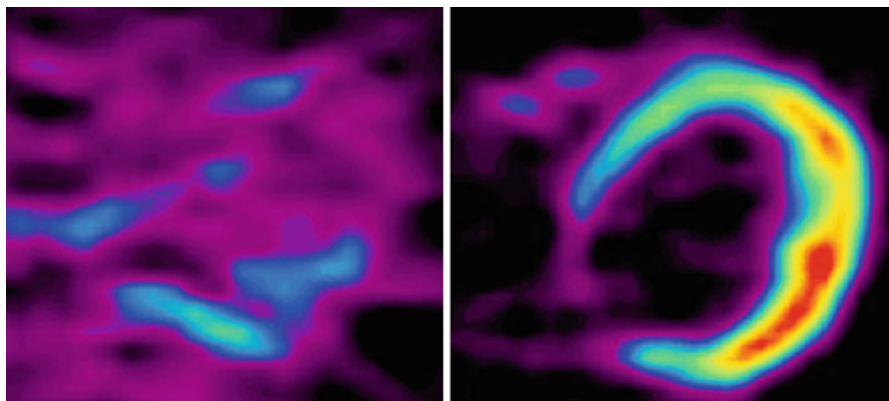


Fig. 20.11 Myocardial metabolism under conditions of sufficient oxygen supply (*left*) and in hypoxia (*right*). In the former case fatty acids are the main metabolic substrate of cardiomyocytes. In hypoxia the rate of beta-oxidation decreases and glucose becomes the prevalent energy source

established that after the medicament blockade of karnitine-transferase the uptake of ^{18}F -FTHA in cardiomyocytes decreased to 87% (Stone et al. 1998). The reverse diffusion of ^{18}F -FTHA and its metabolites from cardiomyocytes is minimal compared with ^{11}C -palmitic acid; therefore, ^{18}F -FTHA is considered as the most suitable RP for quantitative assessment of regional FA utilization rate with help of the universal kinetic model.

20.3.3 The Method of Tomographic Study of Myocardial Glucose Metabolism and Interpretation of the Results

There are three methodologically possible ways of studying ^{18}F -FDG metabolism: on an empty stomach, in presence of artificial hyperglycemia and after medicament reduction of fatty acid concentration in blood plasma. In the normal state, the ^{18}F -FDG PET examination done on an empty stomach detects low RP uptake in the myocardium since it is fatty acids that are the main energy source for cardiomyocytes under conditions of sufficient oxygen supply. ^{18}F -FDG PET examination done on an empty stomach is not informative enough, since in normoxia the myocardium is detected only at the background level and this makes its visualization difficult (Fig. 20.11). For these reasons, ^{18}F -FDG PET is most frequently used after previous oral or intravenous introduction of glucose in order to increase the substrate concentration in blood and correspondingly to augment the concentration of endogenous insulin, which entails higher glucose utilization by cardiac myocytes (Dilsizian 2001).

The method of oral glucose load of 50–100 g glucose 1 h before ^{18}F -FDG injection is the most approved one. In case of the described way of preparation, good-quality myocardial visualization is observed in virtually 90% of cases

(Dilsizian 2001). However, according to other data, an unsatisfactory quality of image occurs in 20–25% of cases in patients with ischemic heart disease, especially in the presence of concomitant diabetes; this causes much difficulty in interpreting the obtained data (Bax et al. 2002; Schinkel 2003). Additional introduction of simple insulin improves visualization in patients with diabetes (Vitale et al. 2001; Bacharach 2003). According to the international recommendations, in order to obtain a good-quality scintigraphic image the blood level of glucose at the moment of ^{18}F -FDG introduction should not exceed 7.0 mmol/L when preparing the patient for the examination by way of artificial hyperinsulinemia (Bacharach 2003).

The method of hyperinsulinemic–euglycemic clamping is well-known; it increases ^{18}F -FDG uptake in the myocardium due to higher glucose utilization by cardiomyocytes, as well as to the suppression of lipolytic processes and decrease in blood level of fatty acids (De Fronzo et al. 1979; Bax et al. 2002; Bacharach 2003). This method permits high-quality images of the myocardium to be obtained, even in patients with concomitant diabetes and to apply quantitative methods of data processing. The procedure of glucose–insulin mixture infusion is long and laborious: constant control of glucose level in blood plasma in the patient is necessary in order to avoid hypoglycemia; the duration of infusion is about 2 h. Nevertheless, this preparation method is the optimum one for patients with pathology of carbohydrate metabolism. Acipimox (a niacin derivative) reduces FFA concentration in blood plasma and thereby increases glucose utilization by cardiomyocytes (Arend Schinkel 2003).

^{18}F -FDG PET of the heart begins with a transmission scan, which usually lasts for 10 min; it is followed by ^{18}F -FDG injection. The 20 min emission scan in case of static data acquisition should be done 45 min after the RP was injected. In some cases, when it is necessary to assess the glucose utilization rate in absolute units, a dynamic scan should be performed. It has the following sequence: 6 frames, 10 s each; 4 frames, 60 s each; 2 frames, 120 s each; 8 frames, 300 s each.

In most cases, ^{18}F -FDG PET of the heart is done in order to assess the viable myocardium. The assessment of PET results is done by the semiquantitative method. In one-isotope examination, the RP uptake in each segment is calculated as a percentage relative to the maximum value. A segment in which the RP uptake makes up $\geq 50\%$ of that in the non-affected myocardium is considered as viable (Rossetti et al. 1995).

However, this method of postprocessing is not free from shortcomings since it does not permit the differentiation of viable myocardium from that partially affected due to subendocardial myocardial infarction.

The method of combined examination of perfusion and myocardial metabolism is more sensitive; it uses *perfusion/metabolism* matching as a viability criterion. There are four scintigraphic variants characterizing *perfusion/metabolism* matching in the myocardium:

1. Normal perfusion conforming to normal ^{18}F -FDG uptake
2. Low perfusion conforming to normal or high ^{18}F -FDG uptake – “*perfusion/metabolism* mismatch” (Fig. 20.12)

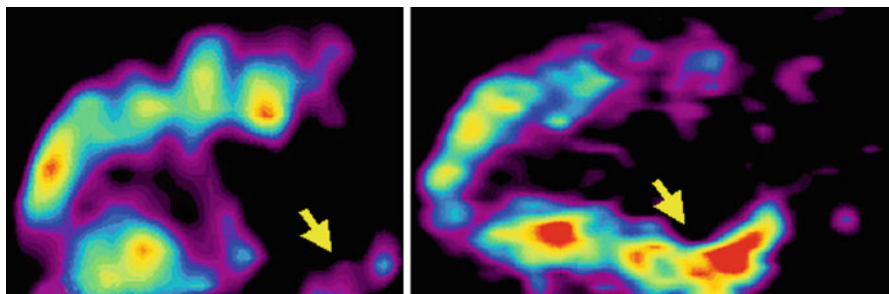


Fig. 20.12 ^{18}F -FDG PET of the heart. Left-ventricular transaxial cuts when examining on an empty stomach (*left*) and under artificial hyperinsulinemia (*right*)

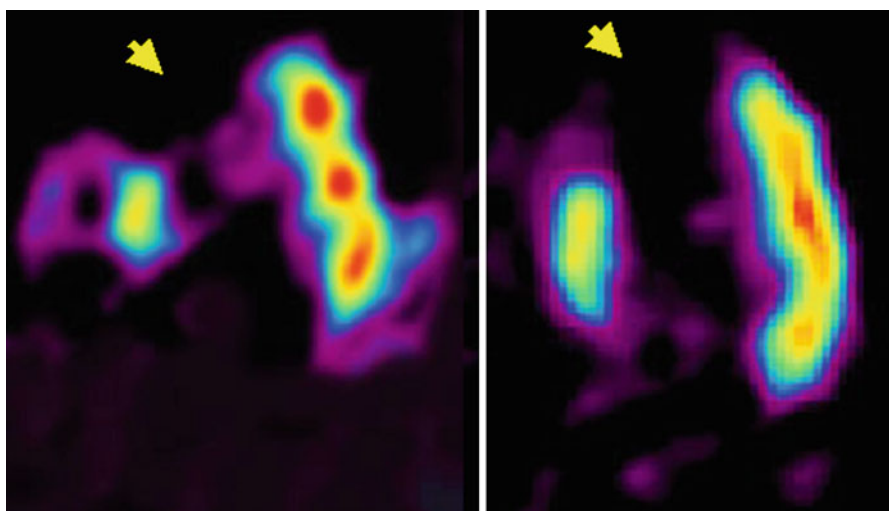


Fig. 20.13 ^{13}N -Ammonia PET (*left*) and ^{18}F -FDG PET (*right*). Horizontal left-ventricular cuts. In the left-ventricular apex an area of matching decrease in perfusion and metabolism is observed (matching defect)

3. Proportional decrease of perfusion and ^{18}F -FDG in the dysfunctional segment – “*perfusion/metabolism match*” (Fig. 20.13) – corresponds to scar
4. Low ^{18}F -FDG uptake conforming to normal perfusion (inverted *perfusion/metabolism mismatch*) (Fig. 20.14)

A dynamic scan is done for the purpose of quantitative analysis, including calculating the glucose utilization rate in cardiomyocytes. A series of frame-by-frame sections along three axes is done analogically to ^{13}N -ammonia PET examination, as described in the previous section. In the last frame, areas of interest are chosen above the left-ventricular myocardium. Then the areas of interest are transferred to all the frames analogically to the examination of myocardial blood flow and time/activity curves are plotted. In order to calculate the dynamics of ^{18}F -FDG concentration in blood plasma in the center of the left-ventricular cavity, areas of interest no

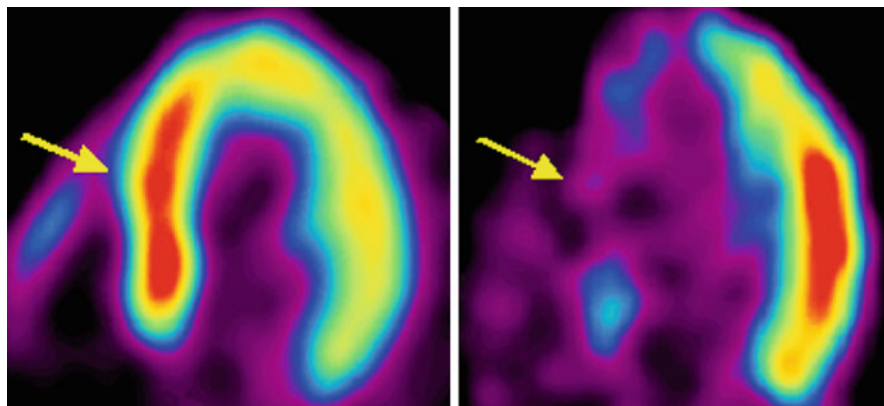


Fig. 20.14 ^{13}N -ammonia PET (*right*) and ^{18}F -FDG PET (*left*), vertical left-ventricular cuts. In the inferior left-ventricular wall an area of marked hypoperfusion is detected combined with glucose hypermetabolism (mismatching defect)

more than 50 mm^2 in size are plotted in two consecutive sections along the short axis on the level of basal segments. The absolute values of the glucose utilization rate are calculated with help of the method developed by Sokoloff et al. (1977).

20.3.4 The Method of Tomographic Examination of Myocardial Fatty Acid Metabolism and Result Interpretation

This method is applied on an empty stomach (at least 6 h of fasting) in order to exclude the negative impact of hyperinsulinemia on the myocardial uptake of labeled acids. Data acquisition is done immediately after the intravenous RP injection in the dynamic regime. The number and duration of scintigraphic frames are determined at will and depend on the particular task.

In the reconstructed cardiac image, the areas of interest are chosen corresponding to the left-ventricular segments and the time/activity curve is plotted. The oxidative fatty acid metabolism rate in cardiomyocytes is reflected in the fast phase of the biexponential curve and the level of fatty acid uptake in the lipid storage of the cell is determined by the slow phase.

As stated previously, the back diffusion of ^{18}F -FTHA and its metabolites from cardiomyocytes is minimal, therefore FA utilization rate can be assessed on the example of ^{18}F -FTHA by means of Patlok's graphic method (Turpeinen et al. 1999).

In an article by Bergmann et al. (1996), it was suggested using a four-compartment kinetic model; on this basis the values characterizing long-chain fatty acid consumption and oxidation in the myocardium are calculated: myocardial fatty acid utilization (MFAU) and myocardial fatty acid oxidation (MFAO) (Bergmann et al. 1996). The first compartment reflects the labeled FA concentration in blood plasma; the second compartment stands for the content of the labeled fatty acid in the interstitial space

and cytosol of the cardiomyocyte, $k1$ is the coefficient determining the fatty acid transmembrane transport rate, $k2$ is the velocity of FA back diffusion. The third compartment includes the labeled fatty acid content in the lipid store of the cell, $k3$ is the coefficient determining the rate of triglyceride and phospholipid formation and $k4$ determines their reverse transformation to fatty acid. Finally, the fourth compartment means the amount of labeled fatty acid subjected to metabolic oxidation in the mitochondria, and $k5$ is the coefficient of fatty acid transport rate to the mitochondria. The labeled fatty acid entrance from blood pool into the cell and the wash-out of labeled metabolites from cardiomyocytes occur proportionally to the blood flow rate. In order to determine the values of the coefficients of the kinetic model it is necessary to know the value of RP concentration in arterial blood (the “input function”). The value of labeled fatty acid concentration in arterial blood can be obtained on the basis of the time/activity curve plotted above the left-ventricular cavity.

The suggested method has become widely used in solving scientific tasks. As for clinical practice, PET examinations with labeled fatty acids are not used in this field.

20.3.5 The Method of Tomographic Examination of Myocardial Oxidative Metabolism

No special preparation is required here. Data acquisition is done immediately after the intravenous introduction of RP in the dynamic regime. The following sequence is usually observed: 12 frames, 10 s each; 5 frames, 1 min each; 3 frames, 2 min each; 1 frame, 10 min. The overall duration of the examination is 33 min.

In the reconstructed image, the areas of interest are selected which correspond to left-ventricular segments; time/activity curves are plotted. The time/activity curves above the myocardium are monoexponential. However, some researchers point out the biexponential character of the graph with short duration of the slow phase. The slope of the monoexponential curve (k_{mono}) or that of the fast phase of the biexponential graph ($k1$) reflect the myocardial oxidative metabolism rate and are in direct correlation to the value of systolic arterial pressure and to the frequency of heart contractions (Schelbert 2004). Kotzerke et al. (1990) found that ^{11}C -acetate clearance is higher in the anterior left-ventricular wall and interventricular septum compared with the lateral wall; it is also stated to be higher in the medium and basal segments than in the apex in the normal state. In another study it was indicated that ^{11}C -acetate clearance is lower in the septum (Buxton 1989a, b). Nevertheless, the detected differences are negligibly small and make up only 7%.

Besides assessing the oxidative metabolism rate, ^{11}C -acetate PET permits calculation of the regional myocardial blood flow rate. In the study of Gropler et al. (Gropler et al. 1991), complete compatibility was detected between the results of PET with ^{15}O -water and those of PET with ^{11}C -acetate in calculating the coronary blood flow rate. In the study of Chan and coworkers, ^{13}N -ammonia PET data were compared with those of PET with ^{11}C -acetate (Chan et al. 1991; Krivokapich et al. 1993).

20.4 Capacities of PET in Assessing the Autonomic Cardiac Innervation

20.4.1 The Structure of the Autonomic Nervous System

Broad functional capacities of the cardiovascular system ensure various adaptation mechanisms, the primary role among them belonging to the neurohumoral regulation. A large number of receptors with different modalities, which are situated in the walls of cardiac chambers and in the epicardium, permit consideration of the heart as an important reflexogenic zone of the organism (Barabanov et al. 2001). The heart is innervated by the autonomic nervous system, consisting of the sympathetic and parasympathetic nerves. In humans the ventricular activity is controlled by both sympathetic and parasympathetic nervous systems, while the atria are primarily under the influence of the parasympathetic part. As is known, the influence of the autonomic nervous system on the cardiac activity is manifested by four main physiological effects: change in frequency and force of heart contractions (the chronotropic and inotropic effects) and regulation of the excitation threshold and of the duration of cardiac cycle phases (the bathmotropic and dromotropic effects).

The afferent fibers of the autonomic nervous system connected with mechanoreceptors are included in the vagus nerves. Free sensitive nerve endings situated immediately under the endocardium are the terminals of afferent fibers included in sympathetic nerves.

The efferent cardiac innervation is also provided by both parts of the autonomic nervous system. The bodies of sympathetic preganglionic neurons are situated in the gray matter of the lateral horns of the three superior thoracic segments of the spinal cord. Preganglionic fibers move towards the neurons of the cervicothoracic (stellate) sympathetic ganglion. The postganglionic fibers of these neurons, together with the parasympathetic fibers of the nervus vagus, form the superior, medium and inferior cardiac nerves. Sympathetic fibers run through the whole organ and innerve not only the myocardium but also elements of the heart conduction system. The distribution of nervous fibers in the myocardium is uneven: the apex and diaphragmatic surface of the heart have less marked innervation than the anterior wall (Shvaley et al. 1992).

The bodies of parasympathetic preganglionic neurons participating in cardiac innervation are situated in the medulla oblongata. They are axons of the vagus nerves. After the vagus nerve enters into the thoracic cavity, branchlets depart from it and are included in cardiac nerves. The derivatives of the vagus nerve are parasympathetic preganglionic fibers, which provide excitation to intramural neurons and further to elements of the conduction system: the sinoatrial and atrioventricular ganglia.

The excitation transmission occurs by way of release of neuromediators from the nerve endings and their interaction with receptors situated on the exterior membrane of the cells of the conduction system and of cardiomyocytes. The main mediator of the parasympathetic autonomic nervous system is acetylcholine, which has affinity to muscarinic receptors. It is muscarinic receptors M2 that are primarily present in

the heart. The neuromediators of the sympathetic autonomic nervous system are adrenaline and noradrenaline. Noradrenaline synthesis occurs in parasympathetic nerve endings from the amino acid tyrosine which is transformed (under the influence of enzymes) into dihydroxyphenylalanine (DOPA) and next into dopamine; the latter accumulates in the vesicles of the presynaptic nerve ending, where it transforms into noradrenaline under the action of the enzyme β -hydrolase. Under the influence of nerve impulses, noradrenaline is released from vesicles; it enters the intersynaptic space and reacts with myocardial adrenoreceptors of the β - and α -subtypes. Under the action of the reverse noradrenaline uptake system, the neuronal noradrenaline transporter, the excess of released noradrenaline is taken up back by nerve endings and accumulated in vesicles or it is destroyed under the effect of the enzyme monoamine oxidase. In the normal state, the prevalence of postsynaptic adrenoreceptors of the β 1-subtype is observed: their share makes up about 80%. However, in some pathologic states, for example in cardiac insufficiency, the number of β 2-receptors grows (Port and Bristow 2001). Alpha-subtype adrenoreceptors are subdivided into postsynaptic ones of the α 1 subtype and presynaptic and postsynaptic ones of the α 2-subtype. The density of α -subtype receptors may grow; in this case the number of β -receptors decreases (Elsinga et al. 2004).

20.4.2 The RPs for Assessing the State of Cardiac Autonomic Innervation

Several classes of RP have been developed by now which are labeled with positron-emitting isotopes for assessing the autonomic innervation of the heart. This opens broad possibilities for detailed study of all the stages of neurogenic transmission (Fig. 20.15).

20.4.3 The RPs for Assessing the State of the Presynaptic Sympathetic Nervous System

The RPs for assessing the cardiomuscular presynaptic innervation are divided into two groups: labeled endogenous catecholamines (^{18}F -fluorodopamine, ^{11}C -epinephrine) and labeled synthetic analogs of catecholamines (^{18}F -6-metaraminol, ^{11}C -hydroxyephedrine, and ^{11}C -phenylephrine). Both groups of RP are widely used in clinical practice.

The pharmacodynamics of labeled endogenous catecholamines reflects all the stages of biochemical transformations of its natural analogs. ^{11}C -Epinephrine is a labeled analog of adrenaline, the adrenal medulla hormone. After its intravenous introduction, ^{11}C -epinephrine enters into blood; with the help of neuronal noradrenaline transporter, it penetrates into the presynaptic nerve endings of sympathetic fibers, where it accumulates in the vesicles of axon terminals and then it is destroyed by monoaminoxidase or catechol-O-methyltransferase. The scintigraphic assessment of the presynaptic sympathetic nervous system by means of ^{11}C -epinephrine

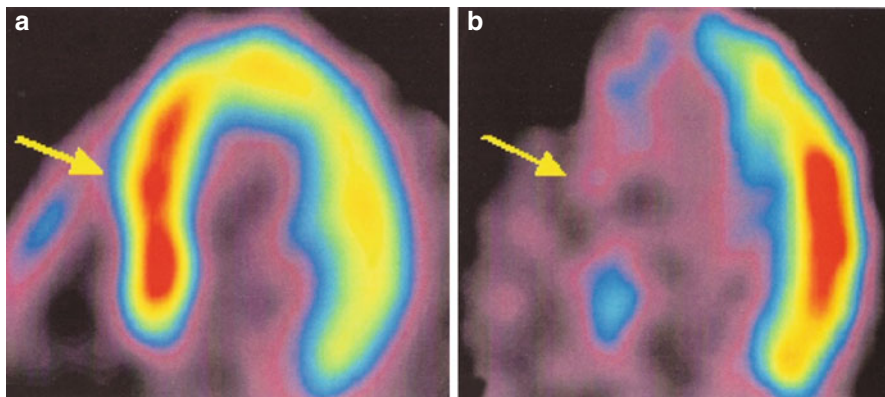


Fig. 20.15 ^{13}N -ammonia PET (left) and ^{18}F -FDG PET (right). Horizontal cuts of the left-ventricular myocardium. An inverted mismatching defect is detected in the interventricular septum characterized by low ^{18}F -FDG uptake with normal uptake of the perfusion RP ^{13}N ammonia (arrow)

consists of determining the evenness of ^{11}C -epinephrine uptake and its catabolism rate. It is done by constructing activity-time graphs above the left ventricle: this reflects the stages of catecholamine transport to nerve endings and the disintegration of catecholamines. On the basis of experimental and clinical research results, ^{11}C -epinephrine has been recognized as the best RP for early diagnosis of neurogenic cardiac dysfunction (Nguyen et al. 1997; Munch et al. 2000).

The properties of ^{18}F -fluorodopamine have been well studied; it has become widely used in diagnosing various neurological diseases. It has been proved on the basis of experimental research that the pharmacodynamics of ^{18}F -fluorodopamine is similar to that of ^{11}C -epinephrine (Goldstein et al. 1990, 1993). After its intravenous introduction, ^{18}F -fluorodopamine is taken up by sympathetic nerve endings; then it enters into a biochemical reaction in axoplasmatic vesicles under the action of the enzyme beta-hydroxylase and accumulates in the form of ^{18}F -fluoronorepinephrine (a labeled analog of noradrenaline). When the sympathetic nervous system is activated ^{18}F -fluoronorepinephrine is released from axon terminals. The clearance of ^{18}F -fluoronorepinephrine is assessed by constructing activity-time graphs above various areas of the left ventricle.

^{18}F -Fluorodopa has been synthesized based on the endogenous mediator dihydroxyphenylalanine (DOPA), which is a biochemical precursor of endogenous dopamine and is transformed into it by way of decarboxylation reaction in nerve endings (Luxen et al. 1990).

Unlike labeled endogenous catecholamines, the RPs which are their synthetic analogs provide information only on a particular stage of neurogenic transmission. In clinical practice, ^{11}C -hydroxyephedrine is the widest used among these RPs. Like ^{11}C -epinephrine, ^{11}C -hydroxyephedrine enters into presynaptic nerve endings of sympathetic fibers under the action of the neuronal noradrenaline transporter and accumulates in vesicles. ^{11}C -Hydroxyephedrine is not destroyed by monoaminoxidase or catechol-O-methyltransferase, therefore this RP only permits assessment of the transport system of

reverse noradrenaline uptake. Clinical research has demonstrated an even distribution and long-term uptake of ^{11}C -hydroxyephedrine in the left ventricle in persons without cardiovascular pathology (Schwaiger et al. 1990a, b). However, a lower uptake and fast excretion of ^{11}C -hydroxyephedrine are observed in case of the intake of desipramine – the specific inhibitor of neuronal noradrenaline transporter (De Grado et al. 1993).

Another labeled synthetic analog of catecholamines is ^{11}C -phenylephrine. Unlike ^{11}C -hydroxyephedrine, it is destroyed in nerve endings under the action of monoamine oxidase, with formation of the labeled metabolite ^{11}C -methylamine, which is rapidly washed out from nerve endings. ^{11}C -Phenylephrine is significantly inferior to ^{11}C -hydroxyephedrine in neuronal transport rate. It has not received wide use in clinical practice.

20.4.4 The RPs for Assessing the State of Postsynaptic Sympathetic Nervous System

The RPs for assessing the postsynaptic sympathetic nervous system are ligands with high affinity and selectivity to adrenoreceptors of the postsynaptic membrane. The main problem faced by radiopharmacists in creating this class of RP consists of searching for non-toxic chemical compounds into which a radionuclide could be included, which would have affinity to a given group of adrenoreceptors and low lipophilicity; additionally, they should not undergo further metabolic transformations after they attach to the receptor.

The labeled non-selective β -antagonist ^{11}C -CGP12177, which has been known since the 1990s, has a high affinity for receptors situated on the surface of the postsynaptic membrane. Fast clearance of this RP from the blood channel, its low uptake in the pulmonary parenchyma and absence of non-specific uptake provide a high-quality PET-image of the heart reflecting the density of β -adrenoreceptors in the myocardium (Van Waarde et al. 1998). As has been demonstrated by Elsinga et al. (1997), information obtained in PET examination of the heart with use of ^{11}C -CGP12177 is comparable in value with the results of myocardial biopsy; unfortunately manufacturing this RP proves to be a complex, laborious and expensive process.

An RP based on the non-selective β -antagonist, ^{11}C -CGP12388, has been synthesized recently, whose pharmacodynamics are similar to those of ^{11}C -CGP12177 (Elsinga et al. 2004). High functional applicability of ^{11}C -CGP12388 demonstrated in a number of experimental studies and clinical trials, combined with fairly simple technique of its radiochemical synthesis, are good reasons for its wide introduction into clinical practice (Momose et al. 2004).

Another non-selective labeled ligand to β -adrenoreceptors is ^{18}F -fluorocarazolol (Berridge et al. 1994). ^{18}F -Fluorocarazolol has the same properties as ^{11}C -CGP12177 and ^{11}C -CGP12388. However, its advantage consists of the inclusion of ^{18}F . The physical half-life period of the ^{11}C isotope is not long (20 min). Therefore, the use of ^{11}C -labeled isotopes is possible only in large PET centers equipped with a cyclotron and a radiochemical laboratory. Meanwhile the half-life period of ^{18}F (109 min) permits transport of the ^{18}F -labeled RP from radiochemical centers to PET-laboratories.

Besides that, another non-selective ligand to myocardial β -adrenoreceptors, ^{18}F -fluorometaraminol, is in the process of preclinical approval.

Currently, only one RP has been developed for assessing the state of α -adrenoreceptors of the sympathetic nervous system; it is based on the labeled analog of the α 1-adrenoblocker prazosine, ^{11}C -GB67. This RP has high affinity for α 1-adrenoreceptors. The maximum uptake of ^{11}C -GB67 in the heart was observed 1–2 min after its intravenous introduction and decreased for an hour (Law et al. 2000). Unfortunately, information on the clinical use of ^{11}C -GB67 in the literature is scarce; its properties should be further studied.

20.5 Clinical Use of PET in Radiological Practice

20.5.1 PET in Studying the Physiology of Coronary Circulation

Coronary flow reserve is an integral index characterizing coronary hemodynamics at the level of large epicardial vessels and microvascular system. A decrease in coronary flow reserve may be observed both in case of the anatomical narrowing of main coronary arteries and in pathology of small intramural vessels, that is their structural (vascular remodeling) or functional (increase in basal tone of the vascular wall due to neurohumoral effects and endothelial dysfunction) changes.

Studies concerning the assessment of coronary hemodynamics report that in persons without cardiovascular pathology, myocardial blood flow both at rest and under pharmacologic tests with vasodilators is uneven. In the work of Chareonthaitawee et al. (2001), based on a large amount of clinical material (160 persons), the spread of values of myocardial blood flow at rest was 0.59–2.05 mL/g/min (the average being 0.98 ± 0.23 mL/g/min). Normal values of coronary flow reserve varied within broad limits (3.753 ± 1.240). Age and sex were mentioned among factors influencing the value of coronary flow reserve. Higher myocardial blood flow at rest was observed in women due to the influence of estrogens on the vascular tone. In the presence of reactive hyperemia, myocardial blood flow was virtually the same in men and women; consequently, the value of coronary flow reserve proved to be lower in women. According to P. Chareonthaitawee, in persons over the age of 65 years, the increase in myocardial blood flow lessens in the presence of hyperemia induced by infusion of vasodilators, which reflects a decrease in coronary flow reserve. In other studies an age-related increase in myocardial blood flow was demonstrated and in consequence a decrease in coronary flow reserve (Collins et al. 1995; Uren et al. 1995). Some studies report simultaneous increase in blood flow at rest and its decreased gain in response to pharmacological vasodilation; this is due to the interaction between mechanical and neurohumoral factors (increase in vascular resistance, decrease in adrenoreceptor sensitivity, disturbance of neurohormonal regulation and endothelial dysfunction) (Duvénoy et al. 1999; Senneff et al. 1991; Lakatta 1993).

Increase in myocardial blood flow in the presence of drug-induced hyperemia depends also on the pharmaceutical substance serving as vasodilator: after the infusion of a standard dose of adenosine blood flow was higher than after the injection

of dipyridamole. According to the results of experimental and clinical research, a pathology of blood circulation is indicated by a decrease in coronary flow reserve down to 2.5 and less (Kaufmann and Camici 2005; Gould 1999). It should be noted that myocardial blood flow in the presence of drug-induced hyperemia and with the use of adenosine or dipyridamole is an integral index reflecting the function of cardiac microvessels on the level of endothelium-dependent and endothelium-independent vasodilation. By influencing A₂-purine receptors of the smooth muscles of the arteriolar vascular wall, adenosine favors their relaxation and therefore provokes direct vasodilatation. On the other hand, this drug has an effect of indirect vasodilation by reacting with A₁-purine receptors and other groups of purine receptors of endotheliocytes; besides that, it provokes flow-dependent vasodilation by inducing the release of nitric oxide, the main endothelium-relaxing factor.

20.6 The Informative Value of PET in Diagnosing Ischemic Heart Disease Induced by Coronary Atherosclerosis

The scintigraphic presentation in patients with post-infarction cardiosclerosis is characterized by stable or partially reversible perfusion defects localized in left-ventricular segments corresponding to infarct-related coronary arteries. In most patients with ECG signs of transmural injury (infarction with Q wave) in the area of scarring stable perfusion defects are observed; this indicates that there is no residual ischemia in the area of post infarction cardiosclerosis. Partially reversible perfusion defects may be observed in patients with ECG signs of Q-infarction and with myocardial infarction without Q wave. Their presence indicates residual myocardial perfusion in the postinfarction area.

In the territory of atherosclerotically changed coronary arteries, perfusion disturbances are usually diagnosed only with help of exercise testing. Absence of perfusion defects at rest, even in presence of hemodynamically significant stenosis, is accounted for by adaptative reaction of coronary vessels, consisting of maximum vasodilation of atherosclerotically changed arteries at the site of stenosis; it is aimed at preventing ischemia of cardiomyocytes.

A number of studies show that PET is the most sensitive method of detecting early changes in coronary arteries and blood flow index closely correlates with the severity of coronary atherosclerosis (Gould 1999; Schelbert 2004; Kaufmann and Camici 2005; De Kemp et al. 2007). It is PET that provides data on the functional significance of coronary stenosis. It has been established that the sensitivity and specificity of PET at rest constitute 84% and 78% respectively when CHD is detected; while under pharmacological stress they are 95–98% and 98–100% respectively (Klocke et al. 2003). This permits to conclude that PET under pharmacological stress is a more sensitive method of diagnosing CHD. In a study of Uren et al. (1994), it was shown that myocardial blood flow during dipyridamole test and coronary flow reserve progressively decrease with increase in degree of coronary arterial stenosis; coronary flow reserve is virtually absent when the degree of stenosis is more than 80%. The authors observed that the value of myocardial blood flow at rest does not depend on the degree of stenosis and does not differ from normal.

Insufficient increase in specific myocardial blood flow under pharmacological dilatation in the basins of stenotic coronary arteries in CHD patients compared with the control group clearly demonstrates the inability of adaptative mechanisms in the coronary blood flow system due to the steal syndrome. Some studies have determined the influence of the geometry of atherosclerotic plaques (and not only that of the degree of coronary arterial stenosis) on the value of coronary flow reserve (Gould et al. 1982; Kirkeeide et al. 1986).

The risk of developing acute coronary complications in the patient group with diffuse atherosclerotic impairment of coronary arteries is higher than in patients with solitary segmental stenoses; therefore its timely diagnosis is very important. Traditional radionuclide diagnosis methods have proved to be little informative: absence of discrete stenoses entails an even uptake of perfusion RP and localized regional perfusion defects are rarely found in such a type of atherosclerotic impairment. The identification of hemodynamically significant diffuse atherosclerotic impairment of coronary arteries by means of X-ray contrast angiography (the “gold standard” in detecting segmental atherosclerosis) is also complex and often gives rise to diagnostic errors. The angiographic signs of diffuse atherosclerosis include the unevenness of the coronary artery wall contour and presence of areas with hemodynamically little significant narrowings, and that does not always corresponds to the real state of things.

The main sign of diffuse impairment of coronary arteries is an even decrease in myocardial blood flow directed from the left-ventricular basal parts to the apex and aggravating under pharmacological test with vasodilators (Gould 1999; Schelbert 2004). Quantitative analysis of PET results serves as a basis for assessing the degree of decrease in coronary flow reserve in various left-ventricular segments; that permits to diagnose the diffuse character of coronary channel impairment and to correctly evaluate its hemodynamic significance.

20.6.1 Characteristics of Coronary Hemodynamics in Persons with Risk Factors for Cardiovascular Complications

20.6.1.1 Myocardial Blood Flow and Coronary Flow Reserve in Patients with Left-Ventricular Myocardial Hypertrophy Related to Arterial Hypertension

Left-ventricular myocardial hypertrophy (LVMH) is characteristic of heart impairment in arterial hypertension and its presence has a significant influence on the course and prognosis of the disease. The development of LVMH in patients with arterial hypertension is associated with a high risk of cardiovascular complications. The results of the Framingham heart study indicate that LVMH is a stronger predictor of an unfavorable prognosis than other known risk factors: the risk of myocardial infarction is four-times higher in patients with LVMH than in those without hypertrophy with comparable level of arterial pressure, and the risk of stroke increases 6–12 times (Levy et al. 1990). It should be noted that LVMH is an important independent risk factor for sudden death, both in men (a sixfold risk increase) and in women (a threefold risk increase) (Kannel 1991).

High risk of cardiovascular complications in patients with arterial hypertension and LVMH is due to various causes, such as the disturbance of diastolic and systolic left-ventricular functions, increase in ventricular ectopic activity and deterioration of coronary circulation. Increased hemodynamic load on the left ventricle is considered to be the leading mechanism of coronary disturbances in LVMH. It provokes an increase in myocardial oxygen demand, disturbance of coronary perfusion induced by compression of intramural arteries by hypertrophied cardiomyocytes and a decrease in number of microvessels per unit of myocardial tissue. With development of myocardial hypertrophy there occurs a reconstruction of the vascular wall structure, including a decrease in size of smooth-muscular arterial tissue and its hardening and the structural reorganization of myocytes and extracellular matrix, which also favors an increase in vascular resistance as well as a reduction in the vasodilator response and in the coronary flow reserve. It has been established that the coronary flow reserve in left-ventricular hypertrophy patients at rest did not differ from normal (Laine et al. 1998; Akinboboye et al. 2004; Gimelly et al. 1998).

At the same time, an insufficient increment in myocardial blood flow accompanying pharmacological vasodilation as well as high coronary vascular resistance in patients with LVMH clearly demonstrate marked functional disturbances in coronary blood flow due to the remodeling of the vascular wall. In studies comparing the PET parameters of coronary hemodynamics and left-ventricular structural changes according to echocardiography, no correlation has been detected between the degree of decrease in coronary flow reserve and the extent of myocardial hypertrophy. This is due to the fact that coronary microvascular impairment develops relatively independently on hypertrophy (Vogt et al. 1992; Pichard et al. 1981; Gimelly et al. 1998). Wrangler et al. (1982) showed that the coronary flow reserve values in LVMH patients are significantly influenced by the duration and severity of arterial hypertension. Also, they found that a disturbance in myocardial blood flow accompanying hyperemia may be spatially heterogeneous. The regional decrease in blood flow in LVMH is accounted for by the effect of local pressure overload and local action of vasoactive substances. In a study by Gimelli et al. (1998), frequent arrhythmic complications in LVMH patients are explained in terms of local disturbances in coronary hemodynamics. The regional disorder of vasomotor function leads to the ischemia of certain left-ventricular segments and to disturbance in electrophysiological processes in these areas, which induces various rhythm disorders. The authors conclude that the spatial unevenness of myocardial blood flow in LVMH patients is a prognostic factor for clinically significant arrhythmia.

According to many authors, concentric left-ventricular hypertrophy is prognostically more unfavorable and it accounts for most cases of coronary complications. Akinboboye et al. (2004) studied the correlation between the left-ventricular geometry, myocardial blood flow, coronary reserve and oxidative metabolism values, as assessed by ^{11}C -acetate PET. The authors have found that myocardial oxidative metabolism is disturbed to a larger extent in concentric LVMH; at the same time no significant differences have been detected between myocardial blood flow and coronary reserve values for different types of LVMH.

According to the PET center of the RSCRST, myocardial blood flow values under vasodilation and coronary reserve in a LVMH patient group were significantly lower in the presence of left-ventricular diastolic dysfunction (127.5 ± 24.4 mL/100 g/min vs 159.2 ± 21.7 mL/100 g/min ($p < 0.05$) and 1.77 ± 0.44 vs 2.11 ± 1.01 ($p < 0.05$), respectively) (Ryzhkova et al. 2005).

20.6.1.2 Myocardial Blood Flow and Coronary Flow Reserve in Patients with Dyslipidemia

Currently there are numerous studies on the connection between the elevated level of cholesterol and its particular fractions, such as low-density lipoproteins, and coronary hemodynamics. In a number of studies, a negative influence of high concentration of common cholesterol on the value of coronary flow reserve has been shown. For example, in a study of Yokoyama et al. (1996a, b), a significant decrease in coronary reserve in patients with the family form of hypercholesterolemia was determined. On the other hand, Pitkanen et al. (1999) demonstrated a decrease in coronary reserve for the IIb phenotype in patients with the family form of hypercholesterolemia, with coronary reserve being within the normal range for the IIa phenotype. In a study of Kaufmann and Gnechchi-Ruscone et al. (2000a, b), the myocardial blood flow values at rest and under dipyridamole infusion did not significantly differ in patients with normal and high common cholesterol levels. Simultaneously, an inverse correlation ($r = -0.61$; $p < 0.01$) was found between the level of low-density lipoproteins and coronary reserve values. Similar results confirming the correlation between high concentration of low-density lipoproteins and myocardial blood flow were obtained by other researchers (Dayanikli et al. 1994; Yokoyama et al. 1996a, b). Most specialists are of the opinion that the main cause of coronary microcirculation impairment in dyslipidemia is endothelial dysfunction. In an experimental work by Hein et al. (1998), it was proved that an increase in titer of low-density lipoproteids provokes a decrease in the release of nitric oxide by endotheliocytes and a rise in synthesis of superoxide anion (a product of cross-oxidation of low-density lipoproteins), which finally leads to an impairment of endothelium-dependent cardiovascular dilation. In its turn, the removal of low-density lipoproteins from blood plasma by way of plasmaferesis improves the endothelial function. The role of endothelial dysfunction in the pathogenesis of coronary microcirculation impairment in patients with dyslipidemia is confirmed by an increase in myocardial blood flow under adenosine test and, correspondingly, that of coronary reserve after a L-arginine intake (this substance is a precursor of nitric oxide) (Drexler et al. 1991; Creager et al. 1992).

As indicated above, the dynamics of myocardial blood flow under cold pressor test reflects the motor function of small vessels and is a highly sensitive test in assessing the function of the endothelium. For example, Schindler et al. (2003) demonstrated a slight augmentation in the area and depth of perfusion defects in patients with dyslipidemia under cold pressor test compared with initial values (before the onset of therapy it was 0.70 ± 0.22 mL/g/min, whereas when under therapy it was 0.77 ± 0.28 mL/g/min), while in the control group myocardial blood flow

clearly increased (0.75 ± 0.17 mL/g/min before the onset of therapy, 1.41 ± 0.34 mL/g/min under therapy).

Treatment with statin medications is known to favor the normalization of the endothelial function. PET studies of myocardial blood flow confirm the increase in coronary reserve in drug-induced hyperemia under statin therapy (Treasure et al. 1995; Anderson et al. 1995; Guethlin et al. 1999). Gould et al. (1994) found a decrease in area and depth of perfusion defects in patients with CHD and dyslipidemia under a 12-week course of hypolipidemic therapy due to the improvement of the endothelial function since a decrease in size of an atherosclerotic plaque is little probable within such a short period of time. Baller et al. (1999) demonstrated an augmentation of coronary flow reserve under efficient 6 month therapy with simvastatin from 2.2 ± 0.6 up to 2.64 ± 0.6 , while myocardial blood flow increased from 182 ± 36 mL/100 g/min to 238 ± 58 mL/100 g/min under drug-induced vasodilation. Yokogama et al. (2004) observed a positive influence of simvastatin on coronary microcirculation; it is noteworthy that no such effect has been found under pravastatin treatment.

The authors explain the detected phenomenon not only by the improvement of the endothelial function but also by regression of diffuse coronary arterial atherosclerosis induced by a decrease in migration and proliferation of smooth-muscular cells and an increase in apoptosis of foam cells after the simvastatin intake. In its turn, simvastatin brings about only the improvement of the endothelial function.

Thus, PET permits to assess the degree of coronary microcirculation impairment in patients with dyslipidemia and to evaluate the efficiency of hypolipidemic therapy.

20.6.1.3 Myocardial Blood Flow and Coronary Reserve in Patients with Long Experience of Smoking

Smoking is an established risk factor for cardiovascular pathologies affecting the peripheric and coronary microcirculation. Smoking induces the development and progression of atherosclerosis as well as the emergence of acute coronary complications by exerting toxic influence on endotheliocytes, decreasing the production of endothelial prostacyclin, provoking adhesion of erythrocytes and platelets, increasing the level of blood plasma fibrinogen and lowering the plasminogen level. Kaufmann and Gnechchi-Ruscone (2000a, b) found a 17% decrease in myocardial blood flow under adenosine-induced hyperemia and a 21% decrease in coronary reserve in a patient group with long smoking experience compared with the non-smoking control group. Campisi et al. (1998) remarked a significant difference between the augmentation of myocardial blood flow under cold pressor test in smoking patients and that in non-smokers (0.78 ± 0.14 mL/g/min vs 0.91 ± 0.18 mL/g/min), while myocardial blood flow values at rest and under dipyridamole-induced hyperemia in smoker and non-smoker groups were comparable (0.68 ± 0.13 mL/g/min to 0.68 ± 0.14 mL/g/min and 1.92 ± 0.38 mL/g/min to 2.04 ± 0.47 mL/g/min). Cigarette smoke contains pro-oxidants, increasing free-radical synthesis, which stimulates low-density lipoprotein peroxidation and inhibiting the activity of the enzyme NO synthetase, responsible for nitric oxide synthesis by endotheliocytes. In some

studies it is reported that even short-term intake of antioxidants may improve coronary hemodynamics. Schindler et al. (2003) demonstrated a significant augmentation of myocardial blood flow under cold pressor test in healthy persons with long experience of smoking who took vitamin C for a short period of time; this was accounted for by an improvement of the endothelial function. In a study by Kaufmann and Gneccchi-Ruscone (2000a, b), a significant increase in coronary flow reserve was observed in smoking patients who received large doses of vitamin C, while no such effect was found in non-smoking patients. Similar results have been obtained under L-arginine therapy: according to PET results, the rates of augmentation of myocardial blood flow in smokers under cold pressor test before and after treatment were $11 \pm 14\%$ and $48 \pm 28\%$, respectively; this rate did not increase in the non-smoker group ($44 \pm 25\%$ and $48 \pm 28\%$, respectively) (Campisi et al. 1998).

20.6.1.4 Myocardial Blood Flow and Coronary Flow Reserve in Women in the Postmenopausal Period

Postmenopause is characterized by the irreversible cessation of menstrual function due to the exhaustion of ovarian follicle function and it is accompanied by a decrease in synthesis of female sex hormones: estrogens and progesterone. In experimental and clinical studies it has been proved that estrogens have a vasodilating effect on peripheric and coronary arteries (Fisher et al. 1997; Fanchenko and Schedrin 1998). Estrogens have a favorable influence on the arterial tone by interacting with specific sex hormone receptors in the vascular wall, depressing collagen synthesis and proliferation of smooth-muscular vascular cells and improving endothelial function. Nevertheless, there are few PET studies on coronary hemodynamics in women in postmenopause. Campisi et al. (2002) showed that menopause has no impact on myocardial blood flow at rest and under dipyridamole-induced hyperemia; however, presence of additional risk factors for cardiovascular diseases leads to a decrease in coronary flow reserve due to an increase in myocardial blood flow at rest and its reduction under drug-induced hyperemia. Insufficient increase in myocardial blood flow in women in postmenopause was observed under cold pressor test independently of additional risk factors. Duvernoy et al. (2004) observed that myocardial blood flow rates at rest and under adenosine test are comparable in women in postmenopause and reproductive periods. In the presence of CHD, a significant decrease in myocardial blood flow was observed under adenosine-induced hyperemia.

The pathogenetic influence of estrogen deficiency on the vascular tone has stimulated studies on the efficiency of substitutive hormonal therapy in women in postmenopause.

Duvernoy et al. (2001) demonstrated the absence of dynamics in myocardial blood flow under cold pressor test and adenosine-induced hyperemia according to ^{13}N -ammonia PET after 3-month combined therapy with hormonal medications (conjugated equine estrogens and cyclic micronized progesterone) in women in postmenopause. It should be noted, though, that the influence of other risk factors for cardiovascular diseases was not taken into account in this study. Campisi et al. (2002) established an interrelation between positive coronary hemodynamics and the duration of hormonal substitutive therapy. A single intravenous injection of

conjugated equine estrogens did not lead to an increase in myocardial blood flow under cold pressor test or dipyridamole-induced hyperemia. At the same time, the increase in myocardial blood flow induced by cold pressor test in women in postmenopause with no risk factors for cardiovascular diseases was significantly higher under long-term hormone therapy compared with the group that did not receive substitutive therapy. At the same time, no significant difference was detected between the positive effects of estrogen monotherapy and those of combined treatment. The authors drew the conclusion of a positive influence of long-term hormone-substitutive therapy on the coronary artery endothelial function in women in postmenopause in absence of additional risk factors.

20.6.1.5 Myocardial Blood Flow and Coronary Flow Reserve in Patients with Diabetes

Cardiovascular pathology is the main factor of high lethality in patients with diabetes. The incidence of CHD and painless myocardial ischemia is higher in patients with diabetes than in the patient population with normoglycemia. The impairment of cardiac vessels in this disease is combined with disturbed autonomic innervation. The specific vascular impairment in diabetes (diabetic microangiopathy) is characterized by the thickening of the basal membrane of capillaries, venules and arterioles, endothelial proliferation, emergence of microaneurisms and endothelial dysfunction. Excessive deposition of PAS-positive substances, premature aging of pericytes and collagen uptake participate in the pathogenesis of basal membrane thickening. Besides the impairment of the microcirculation channel, early development of coronary arterial atherosclerosis is detected. Studies on peripheral blood flow under acute hyperglycemia have clearly demonstrated the disturbance of endothelium-dependent vasodilation developing independently on insulin concentration in blood plasma (Williams et al. 1998; Kawano et al. 1999). The results of experimental and clinical PET research into coronary hemodynamics at rest and under stress tests indicate the significant role of diabetes in myocardial blood flow disorder. Krajer et al. (2003) reported that blood flow values at rest do not differ in patients with type 2 diabetes and in the control group; however, the coronary reserve is significantly lowered in diabetes, which is detected under cold pressor test and dipyridamole test. Similar results were obtained by Hattori et al. (2002) in patients with type 1 diabetes. The authors observe positive influence of therapy with the antioxidant deferoxamine on the vasodilating function of coronary arteries in response to cold pressor test, which justified the conclusion on the influence of free radicals on myocardial blood flow in type 1 diabetes. Di Carli (2003) determined a decrease in coronary reserve in young patients with diabetes both under cold pressor test and under adenosine-induced hyperemia, which suggested the double genesis of microangiopathy: it results from disturbance in endothelium-dependent vasodilation and from the structural reconstruction of the arterial wall. Moreover, no significant difference was observed between myocardial blood flow values in patients of diabetes types 1 and 2. This permitted the authors to infer the leading role of hyperglycemia in the pathogenesis of vasomotor function disorder in diabetes. Physiological hyperinsulinemia in patients with diabetes is accompanied by a 20%

increase in global myocardial blood flow under dipyridamole test (Sundell et al. 2002).

Thus, according to the results of experimental and clinical research, coronary insufficiency in pathological states associated with high risk of cardiovascular diseases is in most cases induced by a disturbance in vasorelaxant endothelial function. Pharmacological therapy aimed at correcting arterial hypertension, dyslipidemia, diabetes or hypoestrogenemia finally removes the endothelial dysfunction and improves coronary microcirculation.

20.6.2 Coronary Hemodynamics in Cardiopathies

20.6.2.1 Myocardial Blood Flow and Coronary Reserve in Patients with Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by hypertrophy of the left-ventricular wall and (seldomly) of the right-ventricular wall without dilatation of the cavity and accompanied by amplification of the systolic function as well as by diastolic dysfunction. In most cases hypertrophy in this disease is asymmetric, with thickening of the interventricular septum being clearly predominant compared with the free left-ventricular walls; this is the anatomic basis for the obstruction of blood outflow from the left ventricle to the aorta. Today HCM is considered to be a primarily genetically conditioned heart disease characterized by a set of specific morpho-functional alterations and by a permanently progressing course with high risk of severe life-threatening arrhythmia and sudden death. The typical morphological alterations include the abnormal architectonics of contractile elements of cardiomyocytes, consisting of hypertrophy and disorientation of muscular fibers, the development of interstitial fibrosis and thickening of the muscular layer of intramural coronary arteries; epicardial coronary arteries usually are not changed. Nevertheless, one of the most frequent symptoms of HCM is exertional angina pectoris. The appropriate conditions for it are present even in the absence of coronary arterial atherosclerosis: an increase in oxygen demand of the hypertrophied myocardium, especially in the period of stress, presence of “muscular bridges,” compressing intramural vessels in systole and in early diastole, and the remodeling of the coronary arterial vascular wall. Therefore, studying the characteristics of hemodynamics in HCM patients is of particular interest. Myocardial blood flow at rest in HCM patients is comparable with those in persons without cardiovascular pathology, but blood flow increase and coronary reserve are lowered under dipyridamole test (Radvan et al. 1997; Kawada et al. 1999). Krams et al. (1998) found a direct correlation between the decrease in diameter of small coronary arteries due to the remodeling of the vascular wall, and the degree of decrease in coronary reserve in HCM patients and angiographically normal epicardial arteries. A number of PET studies have demonstrated a disturbance in vasodilation reserve not only in the hypertrophied interventricular septal myocardium but also in other intact left-ventricular segments. A diffuse disturbance of the vasomotor function of small intramural arteries occurs in HCM in consequence of vascular remodeling and formation

of perivascular fibrosis, which are subsequently confirmed by autopsy (Basso et al. 2000; Maron et al. 1986; Maron 2002). Finally, microvasculopathy in HCMP may be a key stage in the development of syncopal states, left-ventricular dysfunction, ventricular arrhythmia and sudden death. In a study of Cecchi et al. (2003) coronary microcirculation disturbance is considered as an independent risk factor for sudden death.

In a considerable number of HCMP patients the traditional pharmacological therapy does not permit to efficiently influence the symptoms of the disease and does not ensure the optimum quality of life. In such cases, cardiosurgical methods may be applied; in particular transaortal septal myoectomy, which is able to exert a positive influence on the intracardiac hemodynamics and functional disturbances as well as the prognosis of the disease. Seiler et al. (1991) demonstrated an increase in 10-year survivability in patients after surgery of up to 84%, while in those after pharmacological therapy it was 67%. According to PET studies, the septal myoectomy has a positive effect on the regional myocardial blood flow (Jorg-Ciopor et al. 2004). Coronary flow reserve values in the interventricular septum were significantly higher in the patient group after myoectomy than in those patients who received conservative therapy, although the coronary flow reserve in HCMP patients, on the whole, proved to be significantly lowered compared with the control group. The positive effect of myoectomy is due to a decrease in extravascular compression and the improvement of the left-ventricular diastolic relaxation, which is accompanied by improvement of coronary microcirculation. Meanwhile, myoectomy proper cannot have a positive effect on vascular remodeling in HCMP.

20.6.2.2 Myocardial Blood Flow and Coronary Flow Reserve in Patients with Idiopathic Dilatation Cardiomyopathy

Dilatation cardiomyopathy (DCMP) is a polyetiologic myocardial disease based on primary impairment of cardiomyocytes, leading to the impairment of contractile function, dilatation of heart cavities and progressing congestive heart insufficiency. The pathologic anatomical picture of the disease is characterized by an increase in size of the heart cavities; there is always an even thickening of the endocardium; diffuse fibrous-sclerotic changes are usually detected in the myocardium of the left-ventricular free walls and papillary muscles. These changes rarely exceed the limits of the subendocardiac muscular layer and no structural changes are usually observed in cardiac vessels.

The main pathogenetic mechanisms of coronary microcirculation pathology in DCMP consist of disorders of intracardiac hemodynamics, reduction in perfusion pressure and extravascular compression of intramural vessels. In some experimental studies, structural and functional changes in small cardiac vessels are indicated, which are detected as the main disease progresses (Treasure et al. 1990; Inoue et al. 1993; Cannon et al. 1987). In a number of experimental and clinical studies, a decrease in myocardial blood flow has been demonstrated both at rest and under vasodilator tests (Neglia et al. 1995; Canetti et al. 2003). In the 1970s, a group of researches headed by Weiss (1976) demonstrated an interconnection between the value of coronary blood flow and hemodynamic parameters: first of all the frequency

of heart contractions, systolic thickening of the left-ventricular walls and final diastolic pressure. The authors supposed that autoregulation aimed at maintaining the balance between coronary circulation and myocardial metabolic demands is preserved in DCMP patients. In a study by Nowak et al. (2004) the spatial unevenness of myocardial blood flow at rest is reported: the highest values are observed in the anterior left-ventricular wall, while the lowest ones are found in the lateral wall. Neglia et al. (1995) demonstrated a marked decrease in coronary flow reserve in patients with minimal symptoms of heart insufficiency, while no interrelation was observed between the values of final diastolic pressure and coronary flow reserve. On the basis of the obtained results, the authors concluded on the primary structural and functional impairment of small cardiac vessels in DCMP as one of the causes of disturbed coronary hemodynamic in this disease.

The question on the influence of endothelial dysfunction on coronary microcirculation is being widely discussed. In a study by Sun et al. (2000), a double decrease in endothelium-dependent vasodilatation in DCMP patients is reported compared with a healthy volunteer group. However, a more recent study of Stolen et al. (2004) did not find any interrelation between coronary flow reserve values and the degree of increase in blood flow in the brachial artery under the reactive hyperemia test, which would reflect the function of the peripheral vascular endothelium. At the same time it should be taken into account that endothelial dysfunction of peripheral arteries cannot be correctly extrapolated to coronary arteries, which has been proved in studies on comparing the results of reactive hyperemia test and PET in healthy volunteers and patients with CHD and coronary X-syndrome (Bottcher et al. 2001). The results of recent research indicate that coronary microcirculation disturbance in DCMP patients has much prognostic importance; it is an independent predictor of coronary complications and is associated with a high risk of sudden death and progressing heart insufficiency (Neglia et al. 2002).

20.6.3 Capacities of PET with Labeled Fatty Acids in Diagnosing Ischemic Heart Disease

Studying the kinetics of labeled positron-emitting isotopes of long-chain FAs for diagnosing CHD started in the end of the past century. Fox et al. (1985) established in their experimental research that 63% of labeled FA extracted by cardiomyocytes in an unchanged form enters back to the systemic blood flow under conditions of sufficient oxygen supply within 10 min (Fox et al. 1985). Under ischemia conditions the flow of reverse FFA diffusion was significantly higher ($16 \pm 9\%$). A decrease in uptake of ^{11}C -palmitic acid and a slowdown in its clearance in left-ventricular myocardial segments supplied with blood by a stenotic coronary artery compared with intact segments. In their experimental study, Lerch et al. (1982) found slow excretion of ^{11}C -palmitic acid from areas of chronic myocardial hypoxia; however, further change in blood flow rate did not lead to significant changes in clearance of RP. The authors drew the conclusion that slow excretion of ^{11}C -palmitic acid only reflects the biochemical reconstruction of cardiomyocytes

under conditions of insufficient oxygen supply and does not reflect the real oxidative metabolism rate (Lerch et al. 1982). More recent studies demonstrated the possibility of measuring the rate of oxidative metabolism with the help of labeled fatty acids under conditions of ischemia; however the accuracy of these measurements is considerably lower than in the normal myocardium (Schon et al. 1982).

In experimental PET studies with tricarboxylic acid and ^{11}C -acetate, it has been established that RP clearance significantly decreased relative to its initial state after the ligation of coronary artery (Buxton 1989a, b, 1992; Heyndrickx et al. 1993). In areas of experimental myocardial ischemia, a decrease in uptake and excretion of ^{11}C -acetate and high ^{18}F -FDG uptake were observed which indicated a reduction of oxidative metabolism rate and predominance of the anaerobic pathway of glucose utilization. The restoration of coronary blood flow led to gradual normalization of ^{11}C -acetate clearance in accordance with the improvement of regional myocardial contractility. This indicates an interrelation between oxidative metabolism and inotropic function. In patients with ischemic heart disease without old myocardial infarction, ^{11}C -acetate clearance at rest was lower in segments with disturbed regional contractility compared with normokinetic segments. In segments with regional systolic dysfunction, myocardial blood flow rate at rest was within the normal range but a decrease in coronary flow reserve was observed, which suggested a disturbance in oxygen supply and a reduction in oxidative metabolism rate (Vanoverschelde et al. 1993).

In 1984, Grover and coworkers obtained information on the state of FA metabolism in patients with angiographically confirmed CHD under stress-induced ischemia (Grover et al. 1984). The authors established that a decrease in RP uptake and elimination is observed in CHD in the same left-ventricular segments, which correspond to the territory of narrowed coronary arteries. It has also been observed that disturbances in FFA metabolism precede the emergence of electrocardiographic and echocardiographic signs of myocardial ischemia. In a study by Tamaki et al. (1993) a decrease in extraction of ^{11}C -palmitic acid and slowdown in its excretion from myocardial segments supplied with blood by narrowed coronary arteries was observed both at rest and under dobutamine infusion conditions (Tamaki et al. 1993).

A relatively small number of experimental and clinical studies concern the diagnostic capacities of PET with labeled fatty and tricarboxylic acids in diagnosing myocardial infarction. Schelbert (2004) pointed out that a low level of extraction of ^{11}C -palmitic acid and a slowdown in its extraction rate are usually observed in the area of cardiomyocardial impairment, which suggests a decrease in the rate of FA oxidative metabolism and excessive uptake of FA in the stored lipids (Schelbert 2004). ^{11}C -Acetate clearance was significantly lowered in the area of transmural myocardial infarction and in the periinfarction area compared with intact myocardium (21% in the central infarction area, 68% in the periinfarction area relative to intact segments) (Walsh et al. 1989). Studies of Buxton (1989a, b) have shown that ^{11}C -acetate clearance was higher in myocardial segments with disturbed perfusion and high ^{18}F -FDG uptake compared with those with decrease in perfusion and glucose utilization; this suggested the preservation of

oxidative metabolism in these areas. Positive linear dependence has been found in patients between the rate of myocardial blood flow and ^{11}C -acetate clearance in the peri-infarction area.

Interest in fatty acids labeled with positron-emitting isotopes has fallen over the last decade due to the appearance of ^{123}I -labeled fatty acid analogs. In the literature there were only a few articles on this subject. Meanwhile, the short half-life period of the ^{11}C isotope permits a decrease in patient radiation exposure and the physiological suitability of ^{11}C -labeled native fatty acid pharmacodynamics do not entitle a complete rejection their use in radionuclide diagnosis.

20.7 Modern Methods of Diagnosing Viable Myocardium in CHD Patients with Systolic Left-Ventricular Dysfunction

Currently the problem of differentially diagnosing local disturbances in left-ventricular contractility is being widely studied; it concerns both reversible disturbances in which cardiomyocytes retain their viability (stunning, hibernation) and those irreversibly induced by fibrous and scarring changes. The viability of the dysfunctional myocardium may have decisive importance in determining the indications for revascularization, along with information on the state of the coronary channel and ejection fraction.

Timely surgical revascularization of viable dysfunctional areas restores their contractility, decreases the probability of acute coronary complications and progressing heart insufficiency, thereby improving the prognosis. Diagnosing viable myocardium is particularly pressing for patients having marked disturbances of systolic function with the ejection fraction being 35% or less, since in this case the risk of surgical intervention is justified by potential improvement of both regional and global contractility of the left ventricle (Fig. 20.16).

Viable myocardium is characterized by several signs, such as the integrity of cell membranes, intact metabolic activity and inotropic reserve. These characteristics serve as the basis for various modern examination methods applied in order to diagnose myocardial viability. Currently SPECT and PET are used for this purpose; they permit to assess the level of myocardial blood flow and metabolic activity; stress echocardiography with dobutamine is used in order to assess the inotropic reserve; MRI is also used.

20.7.1 PET

PET has become widespread in world practice as a method of assessing myocardial viability in CHD. Early PET examinations in CHD patients permitted the conjecture that ^{18}F -FDG uptake in dysfunctional myocardial segments with lowered coronary blood flow indicates their viability; afterwards this was confirmed by numerous studies (Knuuti et al. 1994; Maki et al. 1996; Tamaki et al. 1991).

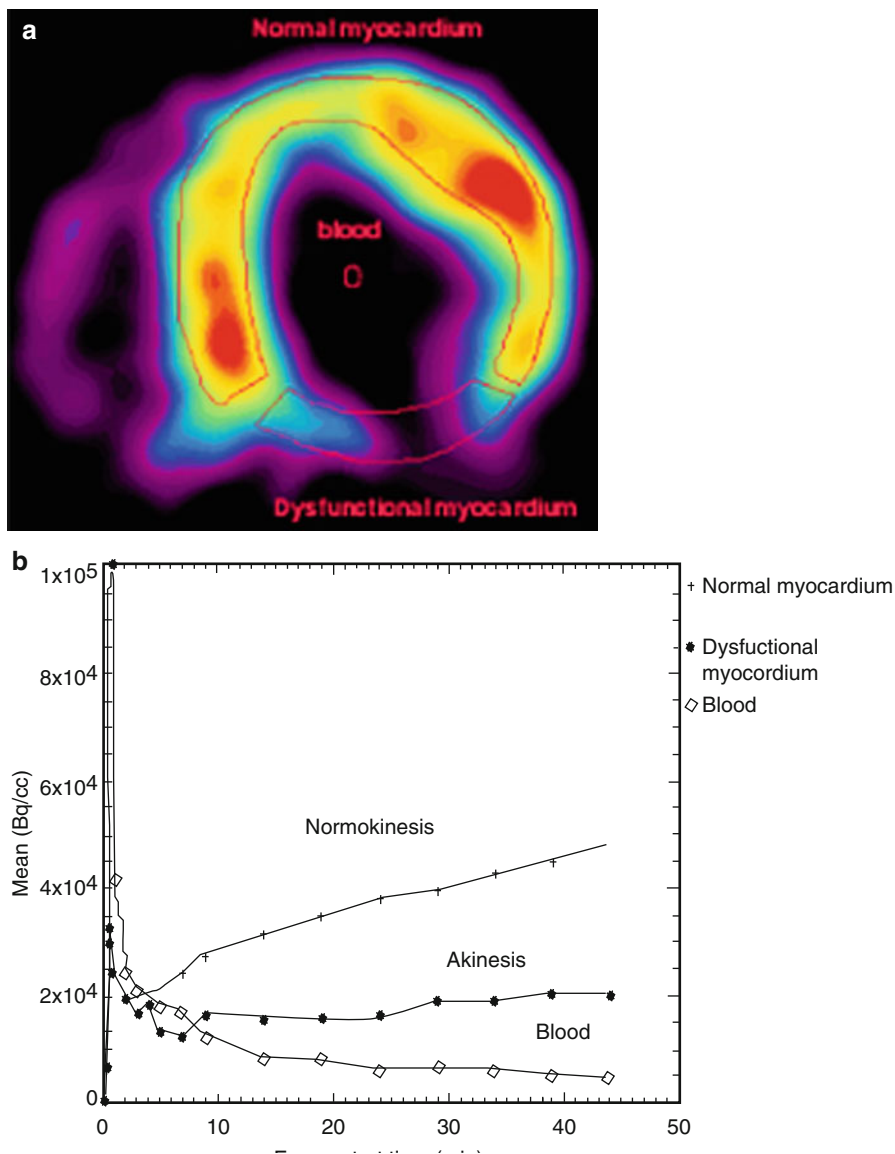


Fig. 20.16 Myocardial cut along the short left-ventricular axis (a). The areas of interest are marked in the left-ventricular cavity and in the myocardium. The myocardial uptake over time reflects myocardial perfusion; higher the uptake, higher the perfusion and that way higher the contractility and opposite as demonstrated in the time-activity graphs (b)

There are two possible methods of examining ^{18}F -FDG metabolism: on fasting and under hyperglycemia. In the normal state a low level of RP uptake in the myocardium is observed in ^{18}F -FDG PET examination done on fasting, since under conditions of sufficient oxygen supply it is fatty acids that are the main energy source

for cardiomyocytes. Schelbert (1994) observed the failure in the attempt of prognosis of contractility recovery in areas of regional left-ventricular dysfunction if the point of reference is intact metabolism in small myocardial segments detected in ^{18}F -FDG PET on fasting. Therefore, methods of hyperinsulinemia are widely used in clinical practice for patient preparation for ^{18}F -FDG PET.

Even though ^{18}F -FDG PET examination of the myocardium is in itself rather efficient in diagnosing myocardial viability, the combined examination of perfusion and metabolism has bigger prognostic value. Marshall et al. (1983) first suggested a method of assessing myocardial viability by way of determining the preservation of ^{18}F -FDG metabolism in dysfunctional segments with lowered perfusion. Bax et al. (2000) observed an improvement in global left-ventricular contractility after revascularization in 85% of perfusion/metabolism mismatch, when the degree of ^{18}F -FDG uptake exceeds perfusion RP uptake more than by 10%. Presence of perfusion/metabolism mismatch is associated with a high risk of coronary adverse events. For example, according to Grandin (1995) in 50% of patients with perfusion/metabolism mismatch coronary adverse events were observed in the course of a year. According to other research, the mortality in the patient group with perfusion/metabolism mismatch was 33–41%, whereas perfusion/metabolism match was associated with 4–12% of death cases. Surgical myocardial revascularization resulted in a decrease in frequency of coronary adverse events by 15% and that in mortality by 12% (Jadvar 1999; Zhang et al. 2001; Schelbert 2004). Thus, the analysis of scientific sources permits a high prognostic value to be inferred for the combined examination of perfusion and glucose metabolism in patients with CHD (Jadvar 1999; Zhang et al. 2001; Bax et al. 1998, 2000, 2004).

The possibility of using PET with fatty acids in diagnosing viable myocardium should be also mentioned. In their study, Lerch et al. (1986) experimentally demonstrated that a slowdown of ^{11}C -palmitic acid clearance in a dysfunctional myocardial segment indicates its ischemization, which in turn is a marker of its viability (Lerch et al. 1986). Soufer et al. (1993) assessed the viability of the stunned myocardium with use of ^{11}C -palmitic acid. Presence of RP uptake with slowdown of its clearance after long-term ischemia indicates metabolic activity in the region under examination and correspondingly it indicates cardiomyocyte viability (Soufer 1993). However, the pharmacokinetics of ^{11}C -palmitic acid under conditions of myocardial ischemia is not a direct reflection of oxidative myocardial metabolism, so the capacities of PET with ^{11}C -labeled fatty acids are quite limited (Lerch et al. 1982; Fox et al. 1985).

There are few studies on the clinical use of ^{18}F -fluorothiaheptadecane acid. Maki et al. (1997) established with help of this RP that fatty acid uptake and beta-oxidation are preserved in viable dysfunctional myocardial segments (Maki et al. 1997). Altenhoefer et al. (1995a, b) described a case when viable myocardium was found by means of ^{18}F -fluorothiaheptadecane acid in the area of the septum, where sharp decrease in ^{18}F -FDG uptake was observed in patients with left bundle-branch block (LBBB), which manifests perhaps some advantages of fatty acids over ^{18}F -FDG in diagnosing viable myocardium in patients with disturbance of intraventricular conduction (Altenhoefer et al. 1995).

LBBB causes considerable difficulties in diagnosing viable myocardium, since in itself the disturbance of intraventricular conduction may lead to local systolic dysfunction in the interventricular septum. Independently of the nature of the intraventricular conduction disturbance, low ^{18}F -FDG uptake by the myocardium of the interventricular septum is observed in patients with LBBB. The causes of regional inhomogeneity of glucose metabolism in cardiomyocytes in LBBB patients have not been completely studied (Altenhoefer 1998; Zanco et al. 2000). The modification of electric potential transmission in LBBB leads to a disturbance in the work of cellular ATP-dependent mechanisms of transmembrane transport of cardiomyocytes in the interventricular septum. The suggested hypothesis explains not only the low uptake of ^{18}F -FDG but also that of the perfusion agent ^{201}Tl -chloride, which enters into the cardiomyocyte under the action of $\text{K}^+\text{-Na}^+\text{-ATPase}$ (Yamada et al. 1990; Le Guludec et al. 1995). Preservation of cardiomyocyte oxidative metabolism in the septum in LBBB patients has been inferred on the basis of ^{11}C -acetate PET results, in spite of low glucose utilization (Lear 1991; Zanco et al. 1998). Altenhoefer et al. (1995a, b) made a successful attempt at diagnosing viable myocardium in LBBB patients with help of labeled fatty acids. The authors established high diagnostic efficiency of PET with ^{18}F -fluorothiaheptadecane acid in LBBB patients compared with ^{18}F -FDG (Altenhoefer et al. 1995). It is reported in the study that high uptake of ^{18}F -fluorothiaheptadecane acid in the septum was observed in this patient category as opposed to low ^{18}F -FDG uptake and so the advantage of labeled fatty acids has been proved in detecting intact myocardial metabolism as a viability marker.

Thus, PET with labeled fatty acids is advisable in patients with intraventricular conduction disorder of the LBBB type in order to assess the volume of viable myocardium.

Myocardial viability assessment with the help of fatty acid is possible only under conditions of sufficient myocardial oxygenation; otherwise, the RP will not be taken up by cardiomyocytes, which will induce false-negative results. In such a situation it is suitable to use ^{18}F -FDG (Sloof et al. 1998). The possibility of using ^{11}C -acetate PET in the diagnosis of viable myocardium and prediction of recovery of contractile left-ventricular function after surgical revascularization has been investigated in many studies. In viable left-ventricular segments relatively intact oxidative metabolism is observed (74–95% clearance of ^{11}C -acetate relative to the intact myocardium) (Gropler et al. 1992). These results confirm once more that the restoration of myocardial contractile function after surgical revascularization depends on the degree of preservation of oxidative metabolism. Gropler et al. (1993) established that the prognostic accuracy in detecting myocardial viability in some patients was higher when ^{11}C -acetate was used compared with ^{18}F -FDG, since in 15% of cases myocardial segments with glucose hypermetabolism were unviable for the reason that anaerobic metabolism was not able to maintain myocardial viability. In Bergmann's opinion, since ^{11}C -acetate utilization does not depend on the predominance of glucose or fatty acids as oxidation substrate and

precisely reflects the oxidative metabolism rate, its use is optimal in assessing myocardial viability (Bergman 1994).

In the literature there is information concerning the diagnostic capacities of PET with labeled acids in patients with various forms of cardiomyopathies. Tadamura et al. (1996) showed that in patients with hypertrophic cardiomyopathy clearance of ^{11}C -acetate is lower in hypertrophied segments than in non-hypertrophied ones. At the same time, the rate of coronary blood flow was the same for both hypertrophied and non-hypertrophied segments.

Mechanisms of FFA metabolism in patients with idiopathic dilatation cardiomyopathy were studied with help of PET with ^{11}C -palmitic acid. In the earliest studies it was established that labeled fatty acid distribution in the left-ventricular myocardium has a diffuse-inhomogeneous character, regional RP uptake defects usually being of small size, moderate severity and situated mosaically (Geltman et al. 1983; Eisenberg et al. 1987). An interesting observation is made in a study by Sochor et al. (1986). In about 50% of patients with idiopathic dilatation cardiomyopathy, an increase in size of RP uptake defect and acceleration of labeled fatty acid elimination were observed in PET with ^{11}C -palmitic acid under artificial hyperinsulinemia. Meanwhile, in the normal state the labeled FA oxidation rate sharply slows down under artificial hyperinsulinemia. The authors came to the conclusion that accelerated wash-out of labeled fatty acids from the myocardium may be related to the replenishment of intermediate products in the tricarboxylic acid cycle in response to glucose entrance into the cell. On the other hand, this process may be due to an increase in reverse diffusion from cardiomyocytes of the labeled fatty acid itself and of its intermediate metabolites.

20.7.2 Alternative Traditional Methods of Diagnosing Viable Myocardium

20.7.2.1 Myocardial Perfusion Scintigraphy

Myocardial perfusion scintigraphy has acquired a reputation as a highly sensitive invasive method of diagnosing viable myocardium. The most approved RP in this field is ^{201}Tl -chloride. Its distribution in the myocardium is proportional to the level of myocardial blood flow. Active ^{201}Tl transport through the cell membrane occurs with the help of $\text{Na}^+\text{-K}^+\text{-ATP-ase}$; therefore its uptake in the myocardium indicates integrity of cell membrane and preservation of the metabolic function. The sensitivity and specificity of the method largely depend on the way of performing myocardial scintigraphy: rest-4-h redistribution, or stress-4-h redistribution-reinjection. When the sequence of rest-4-h redistribution is used, the sensitivity, specificity and diagnostic accuracy of the method constitute 44–93%, 44–92% and 67–80%, respectively. Higher rates of sensitivity, specificity and diagnostic accuracy are obtained when doing myocardial perfusion scintigraphy according to the protocol of stress-4-h redistribution-reinjection (77–100%, 56–80% and 69–91%, respectively) (Sidorenko and Preobrazhenskiy 1997; Lishmanov and Chernov 1997,

2004; Saidova et al. 1998; Belenkov and Saidova 1999). For patients with severe left-ventricular dysfunction it is suitable to perform myocardial scintigraphy according to the rest-4-h redistribution protocol, since stress testing is associated with risk of complications in these patients. While this method is notable for its high sensitivity, its specificity, unfortunately, is insufficient.

An alternative method of prediction of reversibility of left-ventricular dysfunction after myocardial revascularization is myocardial scintigraphy with isonitrile ^{99m}Tc compounds (Belenkov and Saidova 1999; Lishmanov and Chernov 1997, 2004). Isonitrile ^{99m}Tc compounds can be precise markers of myocardial viability, since they reflect the integrity of sarcolemma and preservation of negative mitochondrial gradient, necessary for intracellular RP uptake. During the last decade ^{99m}Tc tracers replaced the traditional ^{201}Tl -chloride due to better availability, lower radioactive load and costs. They can be performed as one or two day protocols or in dual isotope protocols together with ^{201}Tl -chloride.

20.7.2.2 Stress-Echocardiography with Small Dobutamine Doses

Low-dose stress echocardiography possesses the high sensitivity of dobutamine in diagnosing viable myocardium (84% sensitivity, 81.6–90% specificity) (La Canna et al. 1994; Williams et al. 1996).

The sign of viability of dysfunctional segments is the improvement of their contractility when injecting small doses of dobutamine (5–10 $\mu\text{g/kg/min}$) or the so-called biphasic response, when after a temporary improvement of contractility under infusion of high medication doses, areas of regional dysfunction reemerge. Some authors find a more reliable myocardial viability marker in myocardial disposition to ischemization, which is determined only when a protocol with a high dose of dobutamine is performed. The biphasic response or reduction in regional myocardial contractility under high dobutamine doses are more reliable signs of hibernating myocardium than an improvement induced by low doses. Meanwhile, injecting high doses of dobutamine in the presence of marked left-ventricular dysfunction is contraindicated; therefore, the examination has to be limited to small doses. Dobutamine stress-echocardiography should be done with particular caution in patients with ventricular arrhythmia, since injecting even small doses of the medication may induce hemodynamically significant ventricular tachycardia or ventricular fibrillation.

20.8 MRI

There are several ways of determining viable myocardium. Myocardial infarction in the acute stage can be diagnosed on the basis of myocardial tissue edema in the T2-weighted images. However, this method is fraught with risk of false-positive results, since tissular edema is not always a marker of irreversible cardiomyocyte impairment (Bouchard et al. 1989).

The method of assessing viable myocardium by the final diastolic thickness of the left-ventricular wall has a high sensitivity (92%) but a low specificity (Baer et al.

1995). MRI in the cardiosynchronization regime under small-dose dobutamine test has a higher informative value; its sensitivity according to different authors was 77–89%, while its specificity was 94–100% (Baer et al. 1998; Sandstede et al. 1999). However, Gunning (1998) demonstrated low sensitivity of MRI under dobutamine infusion in the diagnosis of viable myocardium (50% sensitivity) in patients with marked systolic left-ventricular dysfunction ($EF > 35\%$), even though it is this patient category that needs correct preoperative assessment of viable myocardial volume (Gunning et al. 1998).

Visualization of unviable myocardium by means of late-enhanced MRI is based on long retention of Gd-DTPA contrast in impaired areas (Hillenbrand et al. 2000; Rehwald et al. 2002). According to Sandstede et al. (2000), the sensitivity of late-enhanced MRI made up 98% and its specificity was 76% (Sandstede et al. 2000). Saeed et al. (2001) compared in their experimental research the results of late Gd-DTPA contrast MRI and those of MRI with the necrosis-specific substance mesoporphine. The authors found that the dimensions of the late Gd-DTPA contrast area exceeded those in mesoporphine examination, which was due to Gd-DTPA being retained in the peri-infarction zone, in which there is always an edema. Rogers (1999) and Kramer (2000) demonstrated an improvement of the contractile function in left-ventricular segments with signs of late contrast in patients with acute myocardial infarction after thrombolytic therapy, which was also due to Gd-DTPA retention in the impaired but potentially viable tissue. Thus, the method of late-enhanced MRI is not specific enough for correctly assessing the volume of unviable myocardium in patients with an acute stage of myocardial infarction.

Kim et al. (2000) demonstrated the high prognostic accuracy of MRI under late contrast-enhancement conditions in predicting the reversibility of myocardial regional contractile function after surgical revascularization in patients with post-infarction cardiosclerosis. The authors determined the threshold of nonviable myocardial area corresponding to 25%; its crossing was not accompanied by an increase in left-ventricular inotropic function after revascularization. The unquestionable advantage of MRI is the possibility of obtaining reliable information on the depth of structural myocardial impairment in the infarction area. The depth of impairment below 25% of the left-ventricular wall thickness is a trustworthy prognostic marker of improvement in regional contractility after surgical therapy.

20.9 PET in Assessing the State of Cardiac Autonomic Innervation in Different Diseases

The disturbance of cardiac autonomic innervation may be observed in different heart diseases. Often an impairment of nerve endings and neurogenic transmission precedes structural and functional pathologic changes in the myocardium; consequently the radionuclide assessment of the state of the autonomic nervous system has an important role in early diagnosis of cardiovascular diseases. Additionally, the results of isotopic methods of examination permit to judge on the efficiency of a number of medications intended for treating various heart diseases.

20.9.1 The State of Autonomic Heart Innervation in Patients with Ischemic Heart Disease

Even short-term myocardial ischemia is known to be able to entail an impairment of nerve endings that is sympathetic remodeling. The sympathetic nervous system of the heart is more sensitive to the consequence of ischemia than cardiomyocytes. Therefore, ischemic defects emerging in the early stages of the disease can be assessed only by means of radionuclide cardiac visualization. According to Spyrou et al. (2002), a decrease in density of β -receptors was found in ^{11}C -CGP12177 PET examination of patients with post-infarction cardiosclerosis. In an experimental study, Schwaiger et al. (1990a, b) on assessing the state of the sympathetic nervous system after 30-min coronary artery occlusion, a considerable decrease in ^{18}F -fluorometaaminole uptake and reduction in noradrenaline concentration were observed in the territory of ligated coronary artery. Friske et al. (2007) weak correlation between the degree of ^{11}C -hydroxyephedrine uptake and coronary flow reserve value was demonstrated. The authors suppose that even a considerable decrease in coronary microcirculation does not lead to the impairment of presynaptic neurogenic transmission. However, in a clinical study by Bulow et al. (2003) contrary data were obtained. The authors established on the basis of ^{11}C -hydroxyephedrine PET results that extended ^{11}C -hydroxyephedrine uptake defects are detected in the left ventricle in CHD patients without prior myocardial infarction, the degree of these defects depending on the severity of coronary atherosclerosis. Similar results confirming the impairment of sympathetic innervations on the presynaptic level of neurogenic transmission were obtained in an experimental study by Luisi et al. (2005). The authors demonstrated the effect of chronic myocardial ischemia on the severity of presynaptic neurogenic transmission impairment, which consisted of the emergence of large ^{11}C -hydroxyephedrine uptake defects in the left ventricle; this suggested a disturbance in the functioning of the transport system of reverse noradrenaline uptake. The assumption was made on the basis of the obtained results that an impairment of reverse noradrenaline uptake may account for the high risk of sudden death in patients with hibernating myocardium induced by chronic ischemia. According to some researchers, left-ventricular segments that underwent sympathetic remodeling due to chronic ischemia are a substrate for life-threatening arrhythmologic complications (Hartikainen et al. 1994; Luisi et al. 2005).

The question concerning the restoration of cardiac sympathetic innervation in persons who underwent myocardial infarction remains disputable. Allman et al. (1993a,b) established a long-term (within 8 months) decrease in ^{11}C -hydroxyephedrine uptake in the post-infarction area, the extension of denervated myocardium significantly exceeding the hypoperfusion area; this confirms once more the high sensitivity of radionuclide cardiac neurovisualization compared with perfusion scintigraphy. However, according to a more recent study by Fallen et al. (1999) done with use of ^{18}F -fluorodopamine, the reinnervation of the impaired segment begins as soon as 2 weeks after myocardial infarction. For this question (prognostically interesting) to be finally solved, further study of the problem is needed on the basis of a large clinical group with use of the available range of RPs reflecting the presynaptic and postsynaptic stages of neurogenic transmission.

20.9.2 The State of Sympathetic Cardiac Innervation in Patients with Diabetes

Cardiovascular disorders such as myocardial infarction, cardiac insufficiency, and stroke are known to be the main cause of high disability and mortality rates in patients with type 2 diabetes (Garcia et al. 1974). The frequency of developing cardiovascular complications in patients with diabetes is three to four times as high as that in persons without carbohydrate metabolism pathology. Besides numerous non-specific risk factors for cardiovascular diseases, the main causes of high morbidity and mortality from cardiac pathology in persons suffering from diabetes are hyperglycemia, hyperinsulinemia, insulin resistance, and progressing cardiac and vascular denervation due to diabetic autonomic neuropathy. The clinical manifestations of the latter may include rest tachycardia, arrhythmias, orthostatic hypotension, left-ventricular dysfunction, painless ischemia and myocardial infarction. Meanwhile, even in the preclinical stage presence of diabetic neuropathy worsens life prognosis and increases the risk of sudden death.

Currently the diagnostic capacities of PET in assessing the state of autonomic cardiac innervation in patients with diabetic neuropathy are well-studied and widely covered in the literature. One of the first studies concerning this problem demonstrated the regional inhomogeneity of ^{11}C -hydroxyephedrine uptake in the myocardium with predominant pathologic affection of the apical, inferior and lateral left-ventricular segments (Allman 1993a. Stevens et al. (1998) found an interrelation between the unevenness of ^{11}C -hydroxyephedrine uptake and the severity of diabetic neuropathy: for middle severity, a decrease in RP uptake was observed only in the distal segments of the inferior left-ventricular wall; while in patients with severe neuropathy, ^{11}C -hydroxyephedrine uptake defects were observed not only in the inferior but also in anterior-lateral cardiac segments. The authors concluded that autonomic dysfunction in diabetic neuropathy is based on disturbance in reverse noradrenaline uptake provoking myocardial electric instability. Additionally, the authors conjecture that treatment with use of beta-blockers should produce a good therapeutic effect. Schmid et al. (1999) demonstrated in their experimental work a close connection between regional disturbance in ^{11}C -hydroxyephedrine reverse uptake in distal left-ventricular segments and low concentration of neuronal growth factor, which permitted to conjecture on the participation of the latter in the pathogenesis of diabetic neuropathy.

20.9.3 The State of Autonomic Cardiac Innervation in Patients with Genetically Determined Ventricular Arrhythmia

First detected ventricular rhythm disturbances are a good reason to examine the cardiovascular system since detecting the cause of arrhythmia determines the correct choice of therapeutical management. The main pathophysiological mechanisms leading to marked electric myocardial instability and ventricular arrhythmia are

structural and functional disturbances of the autonomic nervous regulation of the heart (Shkolnikova 1999; Keefe 1987; Myerlurg et al. 1991). Uneven distribution of nerve endings entails inhomogeneous release of noradrenaline even under physiological conditions, and structural myocardial disorders such as fibrosis, fatty infiltration, cardiosclerosis, etc. aggravate this inhomogeneity. The density of adrenergic cardiac plexes remains stable until the age of 35–40 years old, then their involution begins and after 60–65 years catecholamines in adrenergic nerve endings are not determined by histochemical methods, while cholinergic innervation remains intact (Shkolnikova 1999).

Sympathetic denervation of cardiac tissue leads to hypersensitivity to catecholamine action, which is one of the factors provoking ventricular rhythm disturbances (Inoue and Zipes 1987). The main non-coronary heart diseases accompanied by ventricular arrhythmia are right-ventricular myocardial arrhythmogenic dysplasia, long QT syndrome, Brugada's syndrome as well as cardiomyopathies and tumor formations. In the present chapter we are going to deal with the capacities of PET in diagnosing hereditary diseases accompanied by ventricular arrhythmia.

The newly discovered Brugada's syndrome is an autosomal-dominant type hereditary disease consisting of a set of clinical and ECG signs, namely polymorphous ventricular tachycardia accompanied by syncopal states, complete right bundle-branch block with elevation of the ST-T segment and negative T waves in the right chest leads (Lown 1983; Brugada and Geelen 1998; Brugada et al. 1999; Shimizu et al. 2001). It has been established that Brugada's syndrome is genetically based on a mutation in the *SCN5A* gene in the short arm of the third 3p21–24 chromosome (Wang et al. 2000). This gene encodes the structure of the sodium channel α -subunit protein, sodium channels ensuring the sodium current of the action potential. However, it is supposed that, besides genetic disorders, an important role in arrhythmogenesis in Brugada's syndrome belongs to autonomic nervous system imbalance. Evidence of autonomic dysfunction as being the cause of rhythm disturbance has been obtained in many clinical studies. Kasanuki et al. demonstrated in their work the appearance of typical ECG signs of the disease after propranolol injection and hyperventilation test and their disappearance after exercise stress and isoproterenole infusion (Kasanuki et al. 1997). One of the proofs of parasympathetic influence in Brugada's syndrome is an increase in ST segment elevation amplitude in response to cholinomimatic introduction. In a study by Shimizu et al. (2001) it was established that catecholamine infusion decreases the elevation of the ST segment and in some cases arrests ventricular fibrillation (Shimizu et al. 2001). However, the results of clinical research do not permit to answer the main question on whether parasympathetic nervous system activation or sympathetic system inhibition participate in the arrhythmogenesis in Brugada's syndrome.

Unfortunately, we have found only one article on studying autonomic heart innervations with the use of PET in Brugada's syndrome (Kies et al. 2004). Kias and coworkers demonstrated a high rate of reverse ^{11}C -hydroxyephedrine uptake in patients with Brugada's syndrome compared with the control group, whereas β -adrenoreceptor density determined by means of ^{11}C -CGP12177 was virtually the same in both groups. The authors concluded that one of the mechanisms of electric

myocardial instability is primary sympathetic dysfunction on the presynaptic level, manifesting itself in the high rate of reverse noradrenaline uptake and leading to a marked decrease in concentration of free noradrenaline in the synaptic gap, and finally to a decrease in sympathetic cardiac stimulation.

Arrhythmogenic right-ventricular dysplasia (ARVD) is a family disease of unclear etiology consisting of isolated right-ventricular impairment in the form of fatty or fibrous-fatty myocardial infiltration. The disease is accompanied by ventricular rhythm disorders of different severity, including ventricular fibrillation (Thiene et al. 1988; Sedov et al. 2000). In spite of the fact that structural impairment of the left cardiac segments is not observed in this pathology, presence of left-ventricular myocardial sympathetic denervation has been detected with the help of radionuclide examination methods (Wichter et al. 1994, 1996, 2000).

In a study of Wichter et al. (2000), a decrease in ^{11}C -hydroxyeffedrine and ^{11}C -CGP12177 uptake is shown to occur in the left-ventricular walls, which suggests the inhibition of reverse noradrenaline uptake and decrease in β -adrenoreceptor sensitivity. The authors draw the conclusion that one of the mechanisms of arrhythmogenesis in ARVD is high noradrenaline concentration in the synaptic gap, leading to activation of adenylate cyclase signal system reactions and increase in calcium ion concentration in cardiomyocytes, which provokes ventricular rhythm disorders. Similar results regarding β -receptor density in the left-ventricular myocardium were obtained in a study of Schäfers et al. (2001); at the same time the amount of adrenergic receptors in the pulmonary artery was the same in ARVD patients and in the control group.

Long QT syndrome is a hereditary disease accompanied by prolongation of QT interval in rest ECG ($\text{QTc} \geq 460$ ms), syncopal states and high risk of sudden death due to polymorphous ventricular tachycardia. There are two clinical forms of the long QT syndrome: Romano-Word syndrome with prolongation of QT interval in the ECG, normal hearing and autosomal-dominant inheritance type and Gerwell-Lange-Nilsen syndrome, with a more severe course, congenital bilateral neurosensory deafness and autosomal-recessive inheritance type. The two best studied pathogenetic mechanisms of arrhythmias in long QT syndrome are the following. The first one consists in intracardiac disturbances of myocardial repolarization, namely elevated myocardial sensitivity to the arrhythmogenic effect of catecholamines. The second pathophysiological mechanism is sympathetic innervation imbalance.

The problem of studying the autonomic cardiac innervation in long QT syndrome with use of PET has not been sufficiently covered in literature. Calkins et al. (1993) did not find considerable differences in the rate of ^{11}C -hydroxyephedrine reverse uptake between patients with pathologic QT interval and the control group. However, in a more recent study Mazzadi et al. (2003) demonstrated regional heterogeneity of ^{11}C -hydroxyephedrine distribution in the left-ventricular myocardium in this pathology with lower RP uptake in the anterior and lateral walls and in the interventricular septum. The authors think that disturbance in noradrenaline reverse uptake and consequently high noradrenaline concentration in the synaptic gap, together with elevated myocardial sensitivity to catecholamines in long QT syndrome, are the trigger of ventricular tachyarrhythmia.

Thus, information on studying autonomic cardiac innervation by means of PET in persons with genetically determined noncoronary ventricular arrhythmia is rather scant, and the problem requires further study.

20.9.4 The State of the Sympathetic Cardiac Innervation in Patients with Idiopathic Dilatation Cardiomyopathy

The paramount role in the pathogenesis of cardiac insufficiency is assigned to the activation of the sympathetic autonomic nervous system, whose action has a compensatory character and is oriented at increasing the pumping ability of the heart. However, long-term hypersympathicotonia provokes a number of negative consequences: myocardial ischemia, severe rhythm disorders, ventricular remodeling and activation of cardiomyocyte apoptosis, which finally leads to progressing cardiac insufficiency. So, the radionuclide assessment of the autonomic cardiac innervation is a crucial task for the early diagnosis and prevention of cardiac insufficiency.

In some experimental and clinical studies pathologic changes are demonstrated at the level of postsynaptic neurogenic transmission in patients suffering from idiopathic dilatation cardiomyopathy (DCMP). Merlet et al. (1993) found a significant decrease in ^{11}C -CGP12177 uptake in the left ventricle, which suggested a reduction in density of β -adrenoreceptors, subsequently confirmed by myocardial biopsy results. Similar data were obtained in a study of Jong et al. (2005) on the basis of ^{11}C -CGP12388 PET results. Research in the field of assessing presynaptic cardiac innervations in patients with congestive cardiac insufficiency has demonstrated a marked decrease in ^{11}C -hydroxyephedrine uptake in the left ventricle. Hartman et al. (1999) established the focal character of RP distribution in the left ventricle with prevalent localization of ^{11}C -hydroxyephedrine uptake defects in the apex and apical segment of the inferior wall. A number of experimental and clinical PET studies have demonstrated a disturbance in left-ventricular ^{11}C -hydroxyephedrine uptake in DCMP patients (Ungerer et al. 1998; Vesalainen et al. 1999; Bengel et al. 2001; Pietila et al. 2001, 2002). In a study by Ungerer et al. (1998), correlation was found between the degree of cardiac ^{11}C -hydroxyephedrine uptake and noradrenaline concentration as well as that of its neuronal protein carrier. The authors concluded on the basis of the obtained data that sympathetic remodeling in dilatation cardiomyopathy consists of a decrease in the number of neurons and disorganization of the noradrenaline re-uptake transport system, while reduced ^{11}C -hydroxyephedrine left-ventricular uptake is an early sign of developing cardiac insufficiency. Bengel et al. (2001) studied the interconnection between the systolic left-ventricular function, the state of presynaptic neurogenic transmission and oxidative metabolism rates on the basis of PET results with use of ^{11}C -hydroxyephedrine and ^{11}C -acetate. The authors found that sympathetic innervation disturbance is closely related to the systolic left-ventricular function; this, according to these researchers, indicates the unity of pathogenetic mechanisms of cardiac insufficiency. At the same time, the impairment of the noradrenaline re-uptake transport system did not have any significant effect on the oxidative metabolism rate in cardiomyocytes.

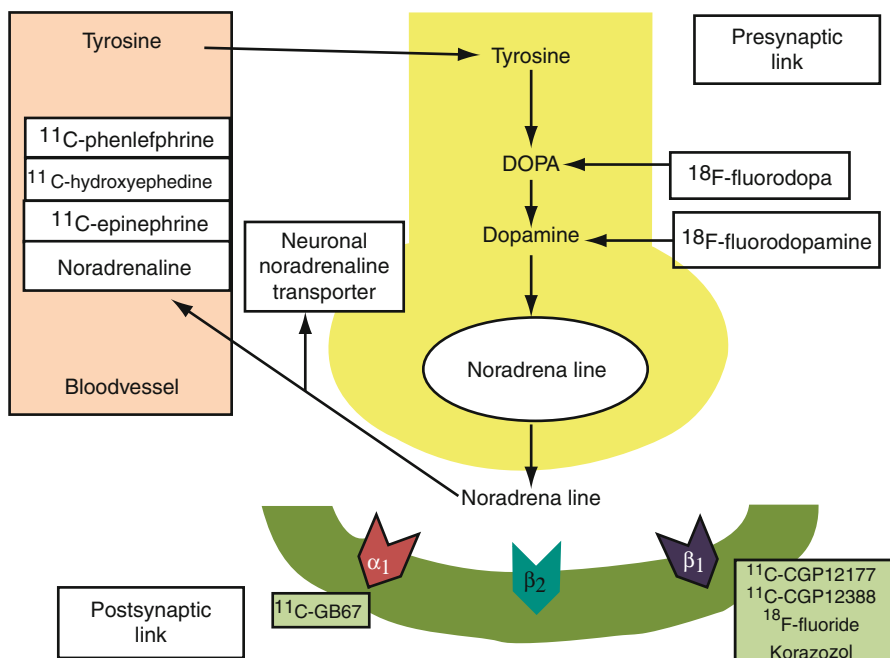


Fig. 20.17 Scheme of sympathetic synapse. RPs for assessing autonomic cardiac innervation

We should stress that along with final diastolic volume and left-ventricular ejection fraction, sympathetic cardiac innervation imbalance in DCM, according to some researchers is an independent prognostic risk factor for sudden death (Fig. 20.17).

20.10 Conclusion

The introduction of PET into cardiological and cardiosurgical practice opens broad possibilities in assessing the pathophysiology of coronary circulation, cardiomyocyte metabolism and autonomic cardiac regulation state. PET is a highly informative method of diagnosing CHD, enabling the objectification of a functionally significant disturbance in coronary microcirculation and to precisely determine the symptom-related coronary artery; this should be taken into account when selecting patients for surgical myocardial revascularization. Non-invasive assessment of coronary microcirculation disorders is also of much importance in risk stratification of cardiovascular complications. PET diagnosis of viable myocardium in areas of left-ventricular dyssynergia permits the differential selection of patients for surgical CHD treatment and prognosis for the recovery of regional and global contractilities after myocardial revascularization. Particular importance of PET should be stressed in objectively evaluating the efficiency of modern pharmacological and surgical methods of treating cardiovascular diseases.

Further development of PET in cardiology is associated with a new generation of visualization techniques. The use of PET-CT scanners permits the study of coronary arterial anatomy and assessment of the degree of coronary calcinosis as well as coronary microvasculopathy and contractile cardiac function within one examination; this opens new prospects for the early diagnosis of coronary heart disease, more precise prognosis and choice of the optimum therapeutic management.

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PET is the most efficient method of noninvasive radiologic study of major biochemical processes and physiological functions of the central nervous system. PET provides valuable information on the state of glucose, amino acid and fatty acid metabolism, cerebral blood flow, penetrability of the hematoencephalic barrier, activity of different enzymes, neurotransmitter synthesis and metabolism, receptor density and gene expression, etc. Changes in these systems may be due to age-specific characteristics, mental, neurodegenerative and cerebrovascular diseases as well as craniocerebral injury. Additionally, PET is rather widely used for studying the pharmacokinetics and pharmacodynamics of drugs applied in modern psychiatric and neurological clinical practice. PET data play an important role in solving many problems of fundamental neurobiology and neurophysiology as well as in further improving the pharmacological and surgical therapy of psychoneurological diseases.

The brain is actively supplied with blood and has an intensive energy metabolism. Even though the brain makes up only 2% of the body weight, in the normal state of the organism it consumes about 20% of absorbed oxygen and 60% of glucose, which is completely oxidized to form CO_2 and H_2O in the citrate cycle and by way of glycolysis (Fig. 21.1). Virtually the only source of energy in brain cells is glucose, which therefore should permanently arrive. Suffice it to say that more than 95% of adenosine triphosphoric acid (ATP) in neurons is formed by the phosphorylation reaction from a glucose molecule. Only in the case of long starvation do cells begin to use an additional energy source, ketone bodies. Glycogen deposits in brain cells are small. Fatty acids, which are transported in blood plasma in the form of albumin-fatty acid complex, do not reach brain cells because of the blood-brain barrier. Nor can amino acids be a source of energy for the ATP synthesis since there is no gluconeogenesis in neurons. The most energy-intensive process in the cells of the central nervous system is the functioning of transport Na^+/K^+ -ATPase (Na^+/K^+ pump) of cell membranes. The active transport of the Na^+ and K^+ ions compensates for the constant ion flow through ion channels. Also, ATP is used in many biosynthetic reactions.

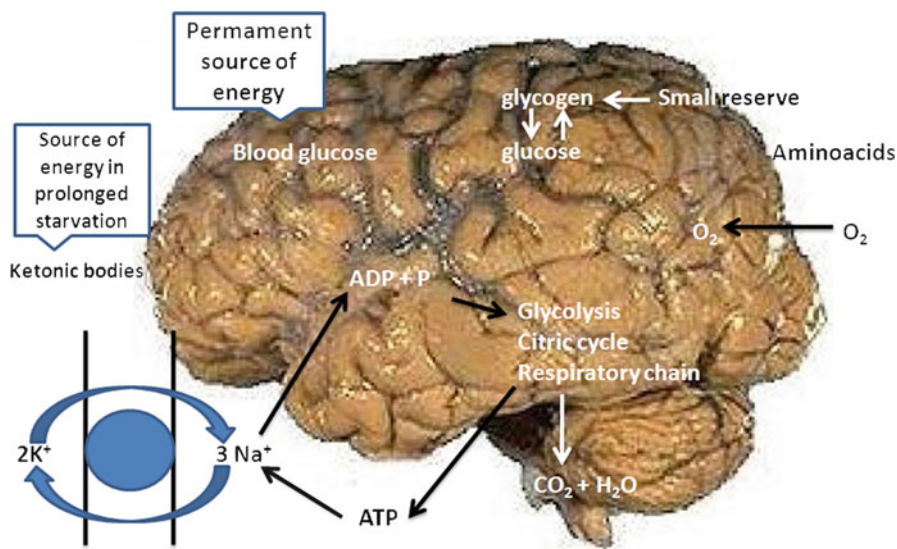


Fig. 21.1 Energy metabolism of the brain

In this context, ^{18}F -FDG is the optimum radiopharmaceutical (RP) for assessing the functional state of the cortex, since it reflects the level of glucose consumption by brain cells (first of all by neurons).

21.1 Some Aspects of PET Image Analysis

Visual analysis is also used in a number of studies. However, more often visual interpretation is supplemented with semiquantitative and quantitative data processing (Medvedev 2008). More accurate information, compared with visual assessment, sufficient for clinical and most scientific studies can be obtained by means of semiquantitative analysis. There are several kinds of data processing with use of semiquantitative image analysis. The simplest kind is determining regional radioactivity normalized to an internal zone of reference. The contralateral area or brain activity on the whole may serve as reference. For semiquantitative analysis, the SUV (standardized uptake value) can be also used. However, in some studies it has been shown that the method of calculating SUV is imperfect and in some cases it introduces up to 50% error in assessing brain metabolism (Cremerius 1997).

The so-called spatial normalization is an important aspect of PET image processing. Normalization aims at leveling all the particular anatomic characteristics of the patient's brain by reducing its parameters (e.g., form, size, spatial situation during data collection) to a certain standard (Senda 2000; Gispert 2003). There are two different approaches to image standardization. First of all, the patient's scanograms can be transformed by achieving a precise coincidence of the points of reference (internal markers which are brain contours or sulci) in the obtained PET tomograms

or standard MRI data available in the data base (anatomic normalization). For that purpose a computer brain atlas is used; for example, HBA (Human Brain Atlas) developed by the Department of Neuroscience of Karolinska Institute, Sweden (Hikima et al. 2004).

Another variant is reducing to standard RP distribution in the patient's brain; for example, when studying regional glucose metabolism or cerebral blood flow (functional normalization). Currently the SPM software (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) and NEUROSTAT based on 3D SSP (Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA) improved by Prof. S. Minoshima (University of Washington, Seattle, WA, USA) are used (Minoshima et al. 1995; Gispert 2003; Hikima et al. 2004; Hosaka 2005). It should be noted that this division of standardization methods concerns not only the main principles that underlie them. This does not mean that some elements of anatomical normalization cannot be used in the second group of methods. For example, in NEUROSTAT the method of marker coincidence is used, bicomissural lines serving as markers. Furthermore, in SPM, parameters of PET image deformation can be set by means of MRI scans obtained in the same patient.

In image standardization by means of internal markers such as brain contours or sulci (fissure of Sylvius, central and cingulate gyri, etc.) with use of a computer atlas (e.g., HBA), corresponding image pixels and their averaging are compared. This process is performed in most software packages under the control of an operator. Therefore, this method of image standardization may be useful in the presence of marked anatomic peculiarities of the patient's brain (Hosaka 2005). In the case when RP uptake is used for standardization, the idea on the real situation of the brain structures is largely conventional. For example, the precentral sulcus of a patient may functionally correspond to the same area of another one, even in the absence of anatomic correspondence. In other words, functional brain normalization between subjects by means of the second method group is objective and reliable but precise anatomic coincidence of corresponding structures cannot be quite guaranteed. In spite of that, there are data confirming in most cases the accuracy of comparing anatomic and functional data after image standardization based on the normalization of RP distribution in the brain (Ishii 2001).

The statistical parametric mapping (SPM) was developed in 1988 and presently is the widest spread method of image standardization. Its creation was conditioned first of all by the rapid development of the methods of functional visualization, especially PET. The main method of finding differences between PET data of patients and those of a control group was then comparison of RP uptake in the regions of interest, which were outlined manually (Friston et al. 1991). For this reason, information on functional activity in pixels and voxels situated outside the chosen region of interest was in fact lost. Then these data were processed with the help of multifactor dispersion analysis. The region of interest was used as the level (degree of impact) of factor. This means that the impact on the region of interest of a given diagnosis or therapy was reflected in the region of interest itself and had a non-additive character. In other words, the effect of therapeutic measures was not

allowed for in assessing metabolic and perfusion changes in the region of interest. Meanwhile, treatment is known to have a general impact on functional processes, which shows up in many regions of interest in the brain. This is why in the late 1980s a group of researchers decided to create a way of data processing that permitted the detection of changes on the basis of parametric maps in the absence of information on the precise localization of the pathologic process. This technique was called statistical parametric mapping (SPM) and that was for several reasons. First of all, it completely corresponds to the acronym designating mapping of statistically significant probabilities, the method of processing EEG results (where “SPM” stands for “significant probability mapping”). This technique permits the creation of pseudomaps of P-magnitudes for determining the spatial-temporal organization of the evoked electric response, which makes easier the visual assessment of obtained EEG data. Further, SPM makes it possible to identify and localize differences in EEG images between patient groups and healthy people (Senda 2000). The second reason for this name is related to the history of development of PET. In the 1970s to 1980s, tomograms were obtained out of raw data which reflected a large number of different physiologic processes (oxygen metabolism, oxygen extraction fraction, regional cerebral blood flow). These images were called parametric maps. In fact, these physiologic parameters were a non-linear function of initial data (Huang et al. 1983). A distinction of SPM from these maps consists of the fact that in SPM, distribution is determined on the basis of a null hypothesis (Senda 2000). This means that SPM is based on a statistical data model which permits determination of error and significance of the detected changes (Moustafa and Baron 2008). Thus, SPM converts changes in images into statistical indices. The choice of statistical methods of processing depends on the task set by the researcher. First of all, he should decide on whether to use a *T*-test, for comparing the averages, or an *F*-test, to confront the dispersions of the two general sets.

The methodology of SPM was presented in detail in several reports published in the early 1990s (Friston et al. 1990, 1991, 1993). In the first stage, images are reoriented by way of comparing corresponding scan voxels in order to level artifacts induced by movements of the head. The normal brain of adults is known to have roughly the same sizes and form. However, some individual characteristics are always observed in the form of the topographic situation of the gyri and sulci in the cortical sections or, for example, differences in the shape of the corpus callosum. Therefore, the second stage of preparing images is their spatial normalization. One of the advantages of SPM is the possibility to create by means of software algorithms standard patterns which can be obtained out of scans of the control group and then be used together with available patterns for spatial normalization (Senda 2000; Herholz 2003). Each 3D brain image is transformed so that all the superficial structures precisely coincide with analogous regions of the pattern included in the program. This process (the so-called affine transformation) includes turning, parallel transfer, scale change and non-linear image deformation. Then, scan smoothing is done with consequent voxel averaging relative to the neighboring elements of the 3D image, which permits to increase the ratio of signal/noise. For this purpose, a Gauss filter or (rarer) wavelet image is used (Silverman 1999; Frackowiak 2003).

SPM presupposes characteristics by voxels of data variability with the introduction of compounded factor (global activity) and residual dispersion determination (Frackowiak 2003). For this purpose the general linear model is used, which can be considered as an extension of linear multiple regression for the case of one dependent variable. So the important advantage of SPM is the possibility to take into account the global brain activity in covariational analysis in order to detect specific changes in the region of interest (Stern 1992).

The last SPM version (SPM 8) allows not only the statistic processing of positron emission tomograms but also the analysis of images obtained by means of other functional methods of examination (fMRI, EEG, EMG) as well as fusion of multi-modal data.

In 1995, Minoshima and coworkers suggested a method of projecting functional activity of the cortex (regional glucose metabolism or blood flow) on the surface of the brain in the form of a 3D image (Minoshima et al. 1995). This method was based on the image standardization developed before at Michigan University and has been called SSP (stereotactic surface projection). This analysis was first used for the early diagnosis of Alzheimer's disease. The advantage of this method consists of the possibility to level the discrepancy between RP uptake in the radial direction which remains after standardization in the 3D images. Due to a partial volume effect, the distribution of functional brain activity along the periphery of the cortex reflects the distribution of the gray matter to a greater degree than radioactivity per millimeter of gray matter (Minoshima et al. 1995, 1997; Cross 2000). Therefore, the use of surface projection permits the avoidance of a misestimation of gray matter distribution in the volume of the brain (Minoshima et al. 1995). This technique is based on the idea that the cortex is essentially a 2D plate of sheet structure, curved and convoluted in the 3D space. Therefore, information obtained in the radial profile is insignificant. However, this is right only as regards the cerebral gyri but not sulci. Consequently, the sulci should be unbent and smoothed with the help of software, which is possible only on the basis of MRI data because of insufficiently high spatial resolution of positron emission tomograms. It should be noted that SSP provokes a slightly bigger loss in spatial resolution than does SPM (Hosaka 2005).

Along with the above-described characteristics of 3D SSP, there are some differences in approach to image standardization in the main software packages. For example in NEUROSTAT, differences in size between the patient's brain and the standard pattern designed in the database are leveled by way of linear scaling (zooming). Then, in order to adjust the shape of the brain to the stereotaxic Talairach and Tournoux atlases or to that of Monreal Neurological Institute, nonlinear image deformation along nerve fiber bundles is used. As was said above, the first stage of image standardization in SPM is determination of the optimum parameters of affine transformation (three parameters giving the turn, three giving the parallel transfer [these six parameters determine image movement], three parameters setting scaling and three setting the slope angle of coordinate axes to corresponding coordinate planes in transition from the initial rectangular coordinate system to the non-rectangular one).

Then nonlinear deformation of the shape of the patient's brain is performed usually by way of linear combination of the basis function of the 3D discrete cosines transformation. The adjustment of images includes minimization of the square of difference between the image and the pattern (Frackowiak 2003).

Some studies have shown that in spite of differences in data standardization algorithms, the results of image processing by means of the these two main software packages prove to be comparable (Senda 2000; Frackowiak 2003). For example, the difference between them in determining the localization of a point of interest does not exceed 1.5 mm with PET solving capacity of 5–6 mm. However, 3D SSP is used more seldomly than SPM. At the same time, its popularity among researchers is gradually growing; for example, this software package, together with the base of volunteers' images presented by Prof. S. Minoshima, are set in the workstations of some of modern PET/CT systems.

There are two kinds of statistical design for examining regional glucose metabolism with the use of intersubjective averaging by way of spatial data normalization. At the same time, it should be noted that for ^{18}F -FDG usually the statistical significance of the influence of the factor affecting the object is studied. The first kind is used in order to determine specific changes in glucose metabolism in patients with different brain diseases. For that purpose the objects of examination are divided into groups ($k(i)$), images (Y) of every patient (i) are obtained and the presence or absence of significant differences in regional glucose metabolism between groups are determined:

$Y_i = \mu + \delta_k + \varepsilon, H_0 : \delta = 0$, where μ is the overall mean, δ is the difference of means, ε is the remainder term (the difference between the given function and the function that approximates it), H_0 is the null hypothesis.

The second kind is used for assessing the differences in glucose metabolism depending on the age. For this purpose, patients of different ages ($x(i)$) are examined, images (Y) of every patient (i) are obtained and it is determined whether there is significant correlation between the age and regional glucose metabolism:

$Y_i = \mu + \delta_x + \varepsilon, H_0 : \delta = 0$, where μ is the overall mean, δ is the difference of means, ε is the remainder term and H_0 is the null hypothesis (Senda 2000).

The quantitative analysis of images is based on biologically grounded mathematical models, which show the radioactivity uptake in the compartments. The latter may reflect both physiological interfaces (vascular space, hematoencephalic barrier and cytoplasm neuron membrane, and others) and biochemical processes (enzyme anabolism and catabolism, transport molecules, receptor proteins). These models should necessarily represent simplified but really existing biological systems or processes.

Initially the quantitative assessment of glucose utilization in the brain was done by the Kety-Schmidt method, developed in 1944, by way of consistent definition of the overall blood flow and difference in glucose content in the arteries and veins of the brain. As is known, almost the whole of the glucose (>90%) in the CNS undergoes aerobic decomposition, therefore glucose and oxygen consumption is measured in parallel (Kety 1950, 1956; Kety and Schmidt 1948). The study of regional glucose utilization with ^{18}F -FDG is based on the method described by Sokoloff

(1977). Initially the method was developed for autoradiography with use of ^{14}C -labeled 2-deoxyglucose. Later on, in 1979 Phelps and coworkers suggested measuring the level of glucose consumption in humans with the help of ^{18}F -FDG (Phelps et al. 1979). In early works on regional glucose consumption, it was detected that the overall brain metabolism utilizes roughly 5.5 mg glucose/min/100 g. This rate may vary from 3.6 to 5.2 mg glucose/min/100 g in the white matter to 5.8–10.3 mg glucose/min/100 g in the gray matter. It is also accepted in the scientific literature to measure glucose consumption in mmol/min/100 g. This allows stoichiometric comparison with concentration of other substances consumed by the brain (e.g., oxygen or ketone bodies). Grams may be converted to moles by means of division of glucose concentration rate in grams by the relative molecular mass of glucose. The absolute values of regional glucose metabolism rate in most of the brain structures remain stable for all age groups.

It should be noted that in spite of high accuracy of quantitative analysis in determining the functional activity of the brain structures, it has not received wide use in clinical practice because of the technical complexity of the procedure and difficult mathematical data processing. Initially the quantitative assessment of brain glucose consumption was performed by the Kety-Schmidt method suggested in 1944, by way of consistent definition of overall cerebral blood flow and difference in glucose content in cerebral arteries and veins (Kety and Schmidt 1948). As is known, almost all glucose in the CNS (>90%) undergoes aerobic decomposition, therefore oxygen consumption and glucose consumption change in parallel.

Cerebral blood flow is traditionally characterized by two indices: blood flow velocity per time unit (for example, mL/min) and tissue perfusion level, which is expressed as blood volume flowing through a certain amount of tissue per time unit (for example, mL/min/100 g). In the brain of a healthy person, blood flow is closely related to the metabolic activity of a given brain structure. This relation is realized by autoregulation mechanisms and is crucial for adequate blood supply of the brain.

The main quantitative parameters of assessing cerebral blood circulation are: cerebral blood flow (CBF), mL/min/100 g; blood volume circulating in cerebral vessels (cerebral blood volume, CBV) mL/100 g; fraction of oxygen extracted by the brain from arterial blood (oxygen extraction fraction, OEF), %; oxygen metabolism rate (OMR), mL/min/100 g and glucose metabolism rate (GMR), mL/min/100 g.

In the same vascular bed, flow rate and glucose consumption rate are virtually in linear relationship. Nevertheless, there can be some differences in ratio of perfusion and metabolism between different basins. For example, since most lateral sections of the neocortex are supplied with blood through the medial cerebral artery, the perfusion level in this area determined with help of H_2^{15}O virtually corresponds to the level of regional brain metabolism measured in the convexital sections. On the other hand, the cerebellum, in spite of low glucose metabolism compared with the neocortex, is characterized by considerably higher perfusion rates.

H_2^{15}O or ^{15}O study of cerebral blood flow is widely used for assessing the activity of cerebral areas participating in neurophysiological processes. The short half-life

period of the radionuclide ^{15}O permits the analysis of changes in functional activity of brain structures in the same subject under different experimental conditions (Wieler et al. 1986). This makes it possible to study such states as rest/motion, wakefulness/different sleep phases, comfort/discomfort or pain, emotional calmness/induced grief as well as anxiety, sexual excitement, fear, irritation. This paradigm of studying brain function is used in a large number of studies aimed at specifying the role of brain structures in processes of thought and behavior, both normal and pathologic. Besides that, the influence of medicines on different sections of the cortex and basal nuclei is studied with the help of H_2^{15}O .

21.2 Dopamine System

In order to study the dopaminergic system, an [^{18}F] fluorinated analog of the dopamine precursor 3,4-dioxyphenylalanine – ^{18}F -DOPA – is used.

DOPA transforms to dopamine with help of the enzyme aromatic amino acid decarboxylase (AAD). Analysis of ^{18}F -DOPA distribution permits assessment of AAD-catalyzed dopamine synthesis in neurons. The level of ^{18}F -DOPA uptake is determined by the following factors: penetration of the RP through the blood–brain barrier, decarboxylation to fluorodopamine and uptake in neuronal terminals. At the same time, this RP does not permit to differentiate whether the detected changes are due to a disturbance in dopamine production activity through terminals or to the general decrease in number of terminals (Volkow et al. 1996; Verhoeff 1999).

A number of models with different degrees of complexity have been suggested for the quantitative analysis of AAD activity by means of PET. Usually the three-compartment model is applied, which reflects the reversible competitive transfer of ^{18}F -DOPA through the blood–brain barrier, its AAD-mediated decarboxylation and uptake, release of fluorodopamine from vesicles, its metabolism and excretion from tissues.

The formation of metabolites beyond the CNS (for example, 3-*O*-methyl- ^{18}F] fluoro-L-DOPA) is also allowed for in mathematical models.

21.2.1 Study of the Activity of Presynaptic Transmitters

Transmitters ensure reverse uptake of dopamine by the terminals of neurons. Having penetrated into the endings of dopaminergic neurons, dopamine catabolyzes in the cell cytosol or accumulates in vesicles by way of active transport (with the help of the so-called vesicular transporter). The study of dopamine transporter permits the indirect assessment of the density of the terminals of dopamine neurons.

In order to study the activity of presynaptic transmitters by means of PET, ^{11}C -labeled or ^{18}F -labeled tropanes are used, such as a dopamine transporter ligand or the cocaine analog [^{11}C] WIN-35, 428 (WIN) (Volkow et al. 1998). However both of them may influence the CNS and interfere with some medicines. Currently the following RPs have been synthesized to study dopamine transport by means of PET:

^{11}C - β -CIT, ^{11}C - β -CFT and ^{18}F - β -CFT. However, it should be noted that the use of these RPs has not become widespread in clinical practice. This is due to the fact that ^{11}C - β -CIT uptake is directly proportional to tissue perfusion. This circumstance makes it difficult to analyse the obtained images and does not permit to objectively assess the intensity of pathologic changes.

The use of ^{11}C - β -CFT, ^{18}F - β -CFT is limited because of the long duration of examination: it takes several hours for the amount of RP necessary for the optimum signal/noise ratio to get bound with the dopamine transporter. Under these conditions, the short half-life period of ^{11}C and ^{18}F does not permit images of good quality to be obtained. In order to study the vesicular monoamine transporter, (+)- α -[^{11}C] dihydrotetrabenazine (DTBZ) is used (Soucy et al. 1997). However, the vesicular monoamine transporter is not a selective transporter for dopamine and is localized also in the terminals of noradrenergic and serotonergic neurons.

21.2.2 Study of the Postsynaptic Level of the Dopaminergic System

In order to assess the density of D receptors, ^{11}C -NNC-112 and ^{11}C -raclopride are used. These pharmaceuticals, along with specifying the receptor number, also permit assessment of the dopamine concentration in the postsynaptic fissure. The method is based on the ability of medicines (for example, D-amphetamine) to cause dopamine release from the terminals, in consequence of which dopamine concentration in the synapse increases and it starts to compete with the RP for the receptor binding site. As a result, the number of receptors bound with RP decreases. This method is used for detecting changes in sensitivity of the terminals of dopamine neurons, both normal and in different pathologic states (Laruelle 2000).

Besides the indicated RPs, ^{11}C -methylspiroperidol or ^{18}F -methylspiroperidol are used for assessing the state of D_2 receptors (MacGregor et al. 1987).

21.3 The Serotonergic System

In studies on serotonin [^{11}C] α -methyl-L-tryptophan is currently used. Under the effect of the enzyme tryptophanhydroxylase, it is transformed to α -methylhydroxytryptophan, then its decarboxylation (with participation of AAD) and transition to α -methylserotonin take place. Unlike serotonin, α -methylserotonin is not catabolyzed by monoaminoxidase and consequently its accumulation level reflects the activity of the serotonin synthesis. The initial studies carried out with the indicated RP have shown significant difference in intensity of serotonin synthesis among volunteers (for example, depending on the sex, presence of migraine in the anamnesis, etc.) (Chugani et al. 1998). In subsequent studies on animals, it has been demonstrated that [^{11}C] α -methyl-L-tryptophan transport and uptake in the brain largely depend on the concentration of large neutral aminoacids in blood plasma and in cerebral matter (Chugani et al. 1999; Shoaf et al. 2000).

21.3.1 Study of the Activity of Presynaptic Transporters

In order to study the density of serotonin transporter, inhibitors of reverse serotonin uptake are used – that is antidepressants. ^{11}C or ^{18}F is used as label. However, excessive lipophilicity of these pharmaceuticals and, as a result, high level of nonspecific binding, as well as low clearance limit, their use for PET. These shortcomings are absent in trans-1,2,3,5,6,10- β -hexahydro-6[4-(methylthio)phenyl]pyrrolo-[2.1-a]-isoquinoline ([+]-[^{11}C]McN5652). Researches with use of this RP have detected significant differences in its uptake in different structures of the brain (primarily in the thalamus, hypothalamus, basal nuclei and mesencephalon) (Staley et al. 1998).

21.4 The Cholinergic System

The study of the cholinergic system arouses much interest due to its participation in the pathogenesis of Alzheimer's disease and, to a lesser extent, of schizophrenia and parkinsonism. ^{11}C -Nicotine was one of the first RPs synthesized for studying the cholinergic system of the brain (Muzic et al. 1998). However, its uptake reflects perfusion and blood–brain barrier penetrability to a greater extent than specific binding with acetylcholine receptors. A more selective pharmaceutical is an analog of the nicotine receptor agonist epibatidine (exo-2-(2'-chloro-5'-pyridil) – azabicyclo [2.2.1] heptanes labeled with ^{18}F .

An analog of 3-quinuclidinyl benzilate has been suggested for studying muscarinic receptors (Giindisch 2000).

21.5 Other Neurotransmitter Systems

^{11}C -Flumazenil is an RP of much importance for studying the density of benzodiazepine receptors; it is widely used for diagnosing epilepsy (Koepp et al. 2000).

Besides that, PET is used for assessing mu-opiate and kappa-opiate receptors. In order to assess their density, ^{18}F -cyclofoxy (fluorinated analog of the opiate receptor antagonist naltrexone), ^{11}C -diprenorphine and ^{11}C -carfentanyl are used (Schadrack et al. 1999; Zubieta et al. 2000).

21.6 Use of PET in Diagnosing Different Brain Diseases

21.6.1 Cerebrovascular Diseases

PET has been used for more than 20 years in diagnosing cerebrovascular diseases (Ackerman et al. 1981; Baron et al. 1981). Most often in examining patients with vascular brain diseases, use is made of H_2^{15}O and gaseous ^{15}O (for assessing cerebral blood flow rate) and ^{18}F -FDG (for studying the level of glucose metabolism).

21.6.1.1 Acute Ischemic Stroke (The First 24 h)

Early PET detection of an apparent decrease in oxygen utilization in the acute period of ischemic stroke permits assessment of the presumable minimum final volume of cerebral infarction. It has been shown that the volume of a focus of ischemia with sharply reduced oxygen metabolism rate detected by PET performed during the first 5–18 h after the stroke correlates with the final volume of cerebral infarction according to CT done 1 month after the stroke. However, the size of the area with low OMR values as revealed by PET was smaller than the size of cerebral infarction detected by CT which is due, according to the authors, to the development of irreversible changes in the ischemic penumbra (De Reuck et al. 1997; Heiss 2003).

Early development of hyperperfusion, indicating recanalization of the occluded artery and resumption of blood flow through it, is observed in one-third of patients examined with PET between 5 and 18 h after the stroke occurred. In most cases a considerable increase in OMR is observed, which seems to be caused by postischemic reaction of energy-dependent cell processes. At the same time, the oxygen extraction fraction is considerably reduced in these areas, which suggests the syndrome of excessive perfusion. It should be particularly noted that no morphologic changes are observed in such patients in the area of early hyperperfusion according to CT examination done after the end of the acute phase of the stroke. The area of ischemic penumbra is characterized by a sharp reduction in cerebral blood flow (below 20 mL/100 g/min), apparent OEF increase and moderate OMR decrease. Sharp decrease in OMR with intact cerebral blood flow as well as fast progressing reduction of the elevated OEF down to its minimum values suggest irreversible changes in the area of ischemic penumbra. As a rule, the outcome of the ischemic penumbra is decided during the first hours of ischemia; however, in some cases it may persist longer, at least up to 16 h (Sobesky et al. 2006).

An assessment of the interrelation of changes in hemodynamics and metabolism, as detected by PET, with clinical outcome of ischemic stroke has been done by Marchal et al. (1999). Three variants of changes have been found:

1. A vast cortical-subcortical zone of necrosis
2. An area of ischemic penumbra in the cortex of the big hemispheres with focus of necrosis absent or with a small deep cerebral infarction
3. An area of hyperperfusion with OMR being within its normal values or lowered in a very small brain area

A correlation has been detected between PET data and stroke outcome. In all the patients of the first group, the outcome was utterly unfavorable: the patient's death or gross residual neurological deficiency. In all the patients of the third group, a rapid recovery of lost functions was observed. The outcome in the patients of the second group was diverse and unpredictable: from death to complete regression of neurological symptoms. These observations indicate that the dimensions of the part of ischemic penumbra which undergoes irreversible changes and necrosis may be various. Moreover, the volume of ischemic penumbra that was not subject to necrosis has a large impact on subsequent recovery, thereby confirming that the survival of cells of ischemic penumbra is a crucial point of recovery after the stroke. The

obtained data have demonstrated that the clinical heterogeneity of cerebral strokes (which manifests itself as unpredictability of stroke outcome in each particular case) is conditioned by that of pathophysiological changes in the brain (Marchal et al. 1999).

A sharp local increase in OEF in acute ischemic stroke indicates an autoregulation disorder in this region of the brain. It does not seem to be accidental that reactive arterial hypertension is often observed in such patients. Any additional lowering of systemic arterial pressure will lead to further lowering of central perfusion pressure and, correspondingly, to induce a decrease in cerebral blood flow in the area of ischemia, which can have very unfavorable consequences if this area already is an ischemic penumbra. It is probably for this reason that reduction in arterial pressure in some patients with acute stage of the disease leads to the progression of ischemic stroke. Medication-induced increase in systemic arterial pressure in case of poor perfusion syndrome in some patients with acute ischemic stroke may improve the rates of cerebral hemodynamics and metabolism and lead to regression of neurological symptoms (Moustafa and Baron 2008).

The results of PET examinations have permitted some conclusions to be drawn of much importance for the prognosis of outcome of ischemic stroke and determining indications for a particular kind of treatment; they are also of help in selecting patients for randomized clinical trials aimed at assessing the efficiency of different medicines.

Detecting hyperperfusion within up to 18 h after the stroke may suggest that a spontaneous artery recanalization occurred and almost always implies a favorable outcome. It is not advisable to include such patients into clinical trials of medicines, even though they may receive treatment with drugs of the antioxidant group which facilitates the reduction of brain lesion volume.

The detection of a vast area with very low hemodynamic and metabolism rates later than 6 h after the stroke occurred indicates an unfavorable prognosis with high risk of developing massive brain edema and early death of the patient. Such patients should also be excluded from clinical trials. Nevertheless, since vasogenic brain edema may itself promote a more severe lesion of brain matter in the area of ischemic penumbra, it is expedient to perform anti-edema therapy and/or surgical brain decompression in such patients in the early stages of ischemic stroke (Giffard 2004).

Presence of an area of sharp increase in OEF and decrease in CBF, together with relative stability of OMR, indicates the preservation of ischemic penumbra. Since the outcome of a stroke in such patients in its natural course may be various and is hardly predictable, and since the potential of their recovery depends on the prevalence rate and dimensions of ischemic penumbra, these patients are the best candidates for treatment with neuroprotectors in the frame of clinical trials. Moreover, the detection of signs of ischemic penumbra up to 18 h after the stroke suggests the necessity of revising the conception of a universal therapeutic window limited by narrow time frames (no more than 6 h) as well as the appropriateness of individually assessing the state of brain hemodynamics and metabolism in therapy planning (Ackerman et al. 1981; Marchal et al. 1999).

21.6.1.2 Subacute and Chronic Stages of Ischemic Stroke

In the subacute period of ischemic stroke, the excessive perfusion syndrome is most often observed in the area of necrosis; it may appear as soon as 2–3 days after the stroke and persist for several weeks. Cerebral blood flow gradually increases, usually achieving its normal or even slightly elevated values by the 12–14th days. OEF decreases down to the limit roughly by the 10th day. Increase in CBF is not accompanied by that in OMR, which, on the contrary, in most cases keeps decreasing, which indicates the low efficiency of blood flow recovery in the irreversibly affected brain matter and perhaps reflects the process of neovascularization with disturbed physiological interrelation of hemodynamics and metabolism. In the area surrounding the area of infarction, moderate changes of PET are often (more than 75% of cases) observed. During more or less 2 months, a progressing decrease in CBF and OMR occurs in the area of cerebral infarction (together with its organization and cavity formation); their values finally tend to zero. In the surrounding brain matter, normalization of CBF and OMR is usually observed (Ackerman et al. 1981; Yamauchi et al. 1999).

21.6.1.3 Long-term Hemodynamic and Metabolic Consequences of Ischemic Stroke

Decrease in CBF and OMR as well as that in glucose metabolism are often observed in brain areas distant from infarction in patients who had ischemic stroke. Detection of such areas permits to map the abnormalities in interneuron connections arising in consequence of focal ischemia. All these phenomena are traditionally united under the general name diaschisis, even though very different cell disturbances may be hidden behind this term – from reversible decrease in functional activity to degenerative process; nevertheless they have in common the same picture of metabolic changes. Since some of these disturbances may have a purely functional character, and so be potentially reversible and since they have an impact on the clinical picture and outcome of ischemic stroke, they have been provoking much interest in researchers and clinicians for the last 15 years. Crossed cerebellar diaschisis, consisting of reduction of OMR and glucose metabolism in the cerebellar hemisphere contralateral to the focus of the lesion, is observed in nearly half of patients with cortical or subcortical ischemic strokes (Grubb et al. 1998; Marchal et al. 1999). This phenomenon is most often observed and is more expressed in extensive infarctions in the frontal/parietal cortex as well as in subcortical infarctions with lesion of the internal capsule (Fig. 21.2).

Such a topographic interconnection suggests crossed cerebellar diaschisis occurs in consequence of lesion of cortical-cerebellopontine tracts with transneuronal functional depression. In the acute stage of stroke, the presence of crossed cerebellar diaschisis in the basin of the right middle cerebral artery does not have a material effect on the outcome of stroke. However, its absence in the acute stroke stage may suggest a favorable prognosis since good recovery is observed in such patients. In the chronic stroke stage, crossed cerebellar diaschisis is observed in the basin of

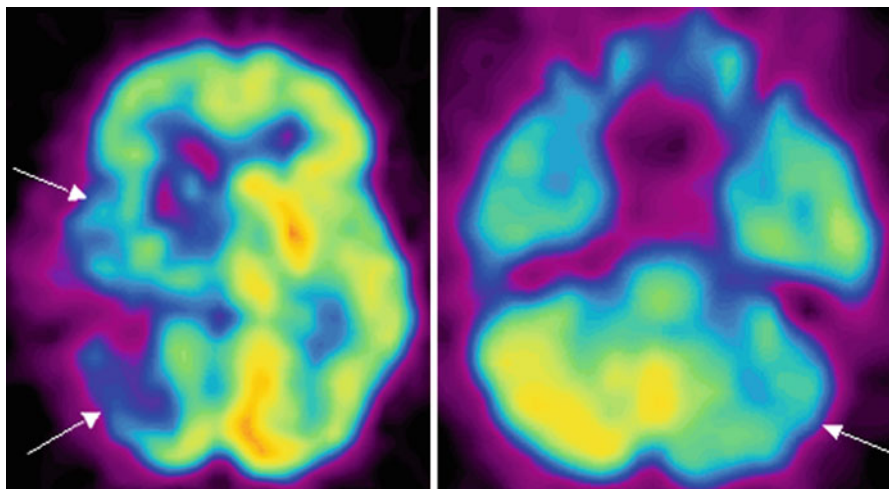


Fig. 21.2 ^{18}F -FDG PET data in a patient with consequences of acute cerebral blood flow disturbance in the basin of the right middle cerebral artery. Reduction in glucose metabolism is observed in the right cerebral hemisphere as well as in the left cerebellar hemisphere contralateral to the area of infarction (crossed cerebellar diaschisis) indicated with *arrows*

blood supply of the middle cerebral artery in cases when no significant clinical amelioration is registered. Reduction in metabolism in the cortical sections of the left hemisphere detected in patients with subcortical strokes and aphasia permitted the supposition that speech disorders may be due to the diaschisis phenomena. Normalization of metabolism rates accompanied the regression of subcortical aphasia.

The diaschisis phenomena in the form of diffuse reduction in metabolism in the cortex of the cerebral hemisphere ipsilateral to the focus are described for lesion in different sections of the thalamus and seem to be due to the lesion of activating thalamic and cortical tracts. Reduction in metabolism, although less marked, may be observed also in the cortex of the contralateral cerebral hemisphere. Since the intensity of metabolic disturbances correlates with the severity of cognitive disorders and no reduction in cortical metabolism is observed in patients with infarctions in the thalamus area in the absence of cognitive disorders, an interconnection between these phenomena can be supposed. Like in subcortical strokes without thalamus lesion, the level of glucose metabolism tends to normalize (concurrently with the recovery of cognitive functions) during several months following the unilateral thalamic stroke. PET examinations permitted to detect metabolic effects spreading backwards, from the cortex into the depth of the hemisphere; for example, marked reduction in metabolism in the striate body and thalamus on the side of the cortical and subcortical stroke (Marchal et al. 1999). PET examinations with use of functional speech loads enable the study of the characteristics of speech recovery and to assess the prospects of this recovery in patients with aphasias. A favorable outcome may be related to partial preservation of language zones in the area of

cerebral infarction in the dominant hemisphere, as well as to reduction of diaschisis in morphologically intact areas of the contralateral hemisphere.

21.6.2 Dementias

21.6.2.1 Glucose Metabolism Study

The first studies on the possibility of using ^{18}F -FDG PET in patients with Alzheimer's disease (AD) were done as far back as in the early 1980s (Benson et al. 1981; Farkas et al. 1982). Recent research has shown that the sensitivity of ^{18}F -FDG PET in diagnosing AD is 88–94% and its specificity is 63–73% (Galton et al. 2000; Fago 2001; Pietrini et al. 2000). PET can be used for predication of cognitive impairments. For example, glucose metabolism decrease in the associative cortex (primarily in prefrontal cortex) indicates with high accuracy the development of cognitive deficiency during the next several years. The posterior associative cortex is situated at the interface of the parietal, temporal and occipital regions. Neurons of the posterior associative cortex have polymodal properties, and they receive information of different modalities: visual, auditory, tactile, kinesthetic. In case of lesion of posterior associative sections, complex forms of space orientation are impaired and performing intellectual operations with participation of spatial analysis is made difficult.

As is known, the prefrontal cortex has a crucial role in ensuring the highest integrative functions. Assessment of the meaning of incoming information, decision making, planning and response are supposed to be realized in this area on the basis of the motivational-emotional and sensory canals.

In Table 21.1, some variants of metabolic changes typical of different nosological forms of dementia are presented (Vander Borghet et al. 1997; Holmes et al. 1999; Imamura et al. 1997; Salmon 1994).

Typical changes detected in some nosological forms of dementias are presented in the Figs. 21.3–21.5.

21.6.2.2 Study of Different Neurotransmitter Systems in Dementias

Dementia with Levy's bodies (DLB) is known to be almost always accompanied by the development of parkinsonism. For this reason, in the differential diagnosis of AD and DLB, ^{18}F -DOPA and other RPs may be used for assessing the dopaminergic system of the brain. DLB is notable for lowered ^{18}F -DOPA uptake in the striatum. The sensitivity and specificity of ^{18}F -DOPA PET in differential diagnosis of AD and DLB constitute 86% and 100% respectively (Silverman 1999).

It has been proved that the disturbance of acetylcholinergic transmission has an important role in developing cognitive disorders in patients with AD (Wenk 2003; Shen 2004). Reduction in acetylcholine content in AD is considered to be due to the degeneration of neurons of the basal nucleus of Meynert; conductive tracts go from it towards many areas of the cerebral cortex (Salehi et al. 1996). Cholinergic neurons of this nucleus are capable of producing acetylcholinesterase, which

Table 21.1 Variants of changes in glucose metabolism in the different nosological forms of dementia

Nosological form of dementia	Typical changes in metabolism in different brain structures
Moderate cognitive impairment	Hypometabolism in the hippocampal formations and posterior cingulate
AD (with early and late onset)	The earliest signs are: hypometabolism in mesial temporal lobes, parietal associative cortex, posterior cingulate. Relative preservation of metabolism in the primary sensorimotor and visual cortices. Intact metabolism of thalami, striatum and cerebellum. In early stages, changes in metabolism may have an asymmetric character; however, with time they always become bilateral.
Discirculatory encephalopathy	Hypometabolism in the frontal lobes, basal nuclei, thalami.
Post-stroke dementia	Numerous foci of hypometabolism in the cerebral cortex, basal nuclei, cerebellum or solitary zones of lowered metabolism or ametabolism in the strategic regions of the brain (parietal-temporal-occipital interface, thalami, frontal lobes, limbic structures).
Dementia with Levy’s bodies	Picture similar to that of AD, but hypometabolism in the occipital cortex (mainly in the primary and associative visual cortex), lenticular nuclei and sometimes in the cerebellum is observed.
Fronto-temporal dementia (e.g., Pick’s disease)	The earliest signs are: hypometabolism in the frontal cortex (including the prefrontal cortex). Here metabolic changes are more marked as compared with lateral temporal and parietal cortices. Relative preservation of metabolism in the primary sensorimotor and visual cortices is characteristic.
Parkinson’s disease, complicated with dementia	Picture similar to that of AD, however changes in the mediobasal regions of temporal lobes are less marked. Metabolism in the visual cortex is less preserved than in AD

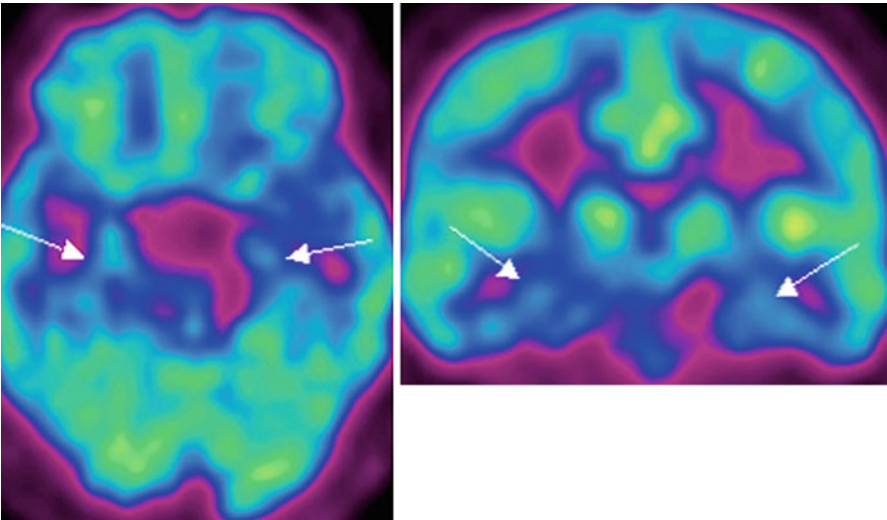


Fig.21.3 ¹⁸F-FDG PET data in a patient with Alzheimer’s disease with early onset. Hypometabolism in the mediobasal sections of temporal lobes is observed (indicated with arrows)

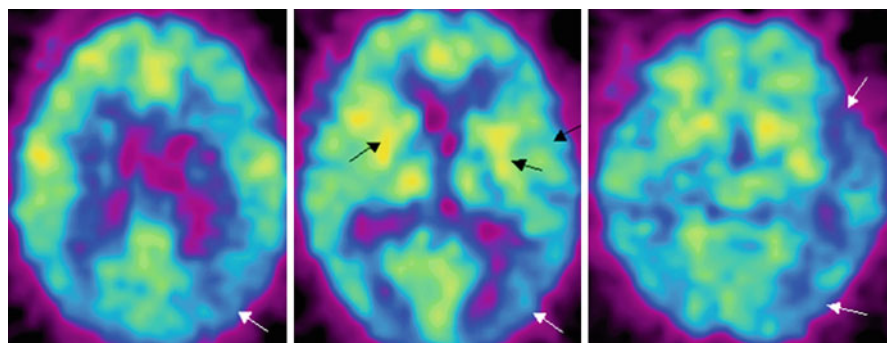


Fig. 21.4 ^{18}F -FDG PET data in a patient with dementia with Levy's bodies. Hypometabolism in the parietal-temporal cortices, occipital lobes, lenticular nuclei is observed, more marked on the left (indicated with arrows)

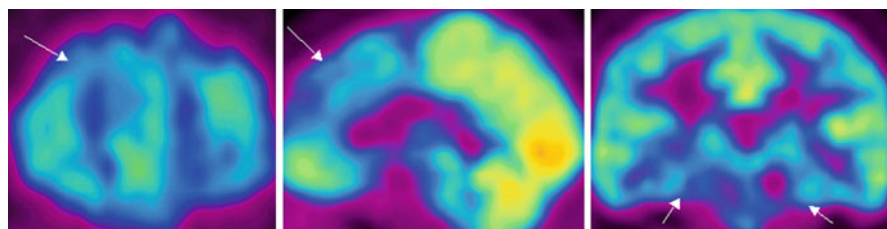


Fig. 21.5 ^{18}F -FDG PET data in a patient with fronto-temporal dementia. Bilateral reduction in glucose metabolism in the frontal and temporal lobes, lenticular nuclei and thalami is observed (indicated with arrows)

destroys acetylcholine. Studies with an analog of ACE, ^{11}C -methyl-piperidine-4-yl propionate (^{11}C -PMP) detect uptake decrease of this RP in the neocortex, hippocampus and amygdaloid body in AD with early onset. In AD patients with late onset, reduction in ^{11}C -PMP uptake is observed in the parietal-temporal region and in the amygdaloid body (Bohnen et al. 2005; Ryu and Chen 2008). A significant correlation has been detected between ACE activity in the cerebral cortex as measured with help of ^{11}C -PMP and the intensity of cognitive changes assessed by means of MMSE. Besides, ACE inhibitors penetrating through the blood-brain barrier are known to have a favorable impact on the clinical state of AD patients. ^{11}C -PNP can also be used in the differential diagnosis between AD and dementia in Parkinson's disease (PD). For example, in PD complicated with dementia, a more marked and diffused decrease in ACE activity (and corresponding decrease in ^{11}C -PMP uptake) is observed compared with Alzheimer's disease (Silverman 1999; Silverman et al. 2001).

21.6.2.3 Study of β -Amyloid and τ -Protein

Currently, specific RPs are being sought for accurate differential diagnosis between AD and other kinds of dementias. It is known that AD is characterized by the development of cerebral amyloidosis with the formation of amyloid plaques. A formed amyloid plaque includes the nucleus and degenerated neurons surrounding it and containing intracellular plexus. The basis of the nucleus of amyloid plaque is composed of pathologic hyperaggregated β -amyloid (42 amino acids) and of a number of additional components (apolipoprotein E, residues of microglia, etc.). Intraneuronal plexuses are hyperphosphorylated τ -protein balls. In its normal state this protein is connected with the system of microtubules and supports the internal structure of neuron. It is supposed that the first initial histopathological changes (in particular, deposition of amyloid plaques) in AD may occur long (10–20 years) before the appearance of the first clinical symptoms. By now several RPs have been synthesized which are capable of binding with β -amyloid plaques. In clinical practice, *N*-methyl[^{11}C]2-(4'-methylaminophenyl)-6-hydroxy-benzothiazol (^{11}C -PIB) is used. Recent studies with use of this RP have shown that significant ^{11}C -PIB uptake is observed in the cerebral cortex and striatum already in the early stages of AD (Koivunen et al. 2008). The intensity of ^{11}C -PIB uptake is in strong inverse correlation with the glucose metabolism rate. However, no interrelation between ^{11}C -PIB uptake and the degree of cognitive disorders has been observed. Research with another specific RP for detecting amyloid and τ -protein, 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malonitrile (^{18}F FDDNP), have shown that even in patients with moderate cognitive deficiency, which precedes AD, an increased uptake of this RP in the temporal, parietal and frontal cortex and in the posterior sections of the cingulated gyri is observed. Changes were detected also in patients in whom ^{18}F -FDG PET and MRI had not found significant disturbances of glucose metabolism and of the cerebral structure (Silverman et al. 2001).

21.6.3 Parkinsonism

21.6.3.1 Study of the State of the Dopaminergic System

In order to assess the state of the presynaptic dopaminergic system (first of all, of the nigrostriatal pathway), which is the first to suffer in PD, ^{18}F -DOPA PET is used. This method makes possible the preclinical diagnosis of PD by way of detecting reduced RP uptake in the striatum, since it is known that by the moment when clinical symptoms of the disease appear, 60–70% of dopaminergic neurons die. This RP reflects the activity of the enzyme dopadecarboxylase in presynaptic dopaminergic terminals as well as the level of dopamine accumulation in neurons of the striatum. In the average a 50% decrease in ^{18}F -DOPA uptake is observed in PD patients in the ventrolateral area of substantia nigra and up to 90% decrease in the putamen (Eidelberg et al. 1990; Ito et al. 2002; Morrish et al. 1996, 1998; Verhoeff 1999). Some authors' data indicate that the use of ^{18}F -DOPA enables not only to detect the decrease in neuronal density and the number of neurons in the striatonigral system

in early stages of the disease but also to predict the development of PD. For example, examinations performed in patients without the clinical symptoms of parkinsonism who were observed for a family form of PD have detected a decrease in ^{18}F -DOPA uptake in the putamen. These data are confirmed by other authors' results of 7-year observation over monozygotic twins with lowered ^{18}F -DOPA uptake in the projection of the lenticular nuclei (Lozano et al. 1998; Verhoeff 1999; Wenning et al. 1997).

Another field of use for ^{18}F -DOPA PET is evaluating the efficiency of PD treatment by means of embryo or stem cell transplantation. For example, comparison of ^{18}F -DOPA PET data and autopsy results has detected a high positive correlation between ^{18}F -DOPA uptake in vivo and tyrosinecarboxylase level in cerebral tissue (Freed et al. 2001). ^{18}F -DOPA uptake rate is in inverse correlation with the degree of motor disorders. At the same time, the correlation between cognitive disorders and dopamine neuron degeneration in these patients is now under discussion. It should be noted that taking levodopa or apomorphine (a strong dopamine mimetic) may induce changes in RP uptake in the striatum. In the early stages of the disease, a decrease in ^{18}F -DOPA uptake by neurons of the striatum occurs in consequence of dopamine autoreceptor activation and reduced activity of the enzyme decarboxylase. Simultaneously increased ^{18}F -DOPA uptake in the dorsolateral prefrontal cortex and anterior cingulate gyri may be detected, which is not observed in the late stages of the disease. This is due to compensatory increase in activity of decarboxylase in the mesocortical dopamine pathway caused by nigrostriatal degeneration. In the presence of pathologic progression, uptake in the striatum and in the indicated cortex may decrease due to progressing degeneration (Lozano et al. 1998; Morrish et al. 1996, 1998).

Use of ^{18}F -DOPA PET has some limitations in patients with early stages of parkinsonism. For example, its use in such patients may provoke an underestimation of the degree of reduction in density of dopaminergic neurons, due to moderate decrease in the dopaminedecarboxylase level. For this reason, most authors suggest using RP selectively binding with dopamine transporter in the early stages of the disease, when its symptoms are poorly marked (Shih et al. 2006; Stoessl 2007; Troiano et al. 2009). In order to assess dopamine neurotransmission, it seems to be preferable to use β -CIT and β -CIT-FP SPECT, since it makes it possible to determine the amount of dopamine transporter in the synaptic fissure with up to 95% specificity. At the same time, in PD and in neurodegenerative diseases accompanied by parkinsonism a reduction in dopamine transporter content in the striatonigral system occurs as soon as in the early stages of the disease (Seibyl et al. 1998; Pirker et al. 2000).

Summarizing, we may state that ^{18}F -DOPA has both advantages and shortcomings in diagnosing parkinsonism compared with other RPs (in particular, ^{18}F -FDG). Its advantages are as follows:

- It permits the detection of neuron losses in the striatonigral system in the early stages of D (preclinical diagnosis).
- It enables prediction of the development of PD (in family forms of the disease).

- ^{18}F -DOPA uptake depends on the degree of motor disorders.
- It makes it possible to assess the efficiency of embryo and stem cell transplantation.

The shortcomings of this RP are:

- In some patients with early PD stages and ill-defined symptoms, false-negative results may be obtained due to moderate dopaminedecarboxylase inhibition.
- ^{18}F -DOPA uptake does not depend on the degree of cognitive disorders.
- It is impossible to make differential diagnosis of neurodegenerative diseases completed by parkinsonism.

^{11}C -Raclopride studies have shown a relative increase in D_2 receptor activity in the putamen and globus pallidus in patients with Parkinson's disease. In the early pathologic stages, ^{11}C -raclopride uptake by striatum neurons may be elevated, while ^{11}C -raclopride uptake in the projection of the caudate heads remains normal. With disease progression, a decrease in receptor number and density may occur in these structures and consequently a reduction of RP uptake. However, usually the RP uptake in the striatum remains within normal limits in these patients. At the same time, in patients with atypical forms of parkinsonism a decrease in D_2 receptor density occurs in the early disease stages. In the initial stages of PD D_1 receptor density is usually elevated. With disease progression, the number of D_1 receptors usually decreases (Piggott et al. 1999; Ito et al. 2002; Kaasinen et al. 2000; Verhoeff 1999). So, summarizing the adduced data, we may state that in PD the quantity of presynaptic dopaminergic endings and the amount of dopamine transporter in the synaptic fissure decrease, while in other neurodegenerative diseases such as multisystem atrophy, progressive supranuclear palsy and corticobasal degeneration the amount of dopamine receptors in the striatum decreases already in the early pathologic stages. On the basis of these data it is accepted to use the terms of presynaptic parkinsonism in case of PD and postsynaptic parkinsonism in multisystem atrophy (MSA) and other neurodegenerative diseases. It should be noted that one of the shortcomings of the mentioned specific RP is the impossibility of differential diagnosis between nosological forms of neurodegenerative diseases accompanied by parkinsonism, since their pathological pictures are virtually the same.

21.6.3.2 Investigating Nondopaminergic Receptor Systems in Parkinsonism

The possibility of studying other receptor systems in patients with parkinsonism arouses much interest. Some authors' research done with the help of ^{11}C -diprenorphine PET has detected a decrease in RP uptake in the striatum, thalamus and anterior cingulate gyri compared with the control group, which was due to a reduction in density of opiate receptors specific for enkephalin and dynorphin. Study of peripheral benzodiazepine receptors as markers of microglia cell proliferation also seems to be promising. Use of ^{11}C -PK11195 tropic to gamma-aminobutyric acid-receptors in PD patients has shown an increase in uptake of this RP in the projection of the substantia nigra and globus pallidus in the absence of

changes in other structures of the striatum. In MSA patients, an increase in ^{11}C -PK11195 uptake was observed also in the putamen and prefrontal cortex. Some studies suggest the possibility of using the serotonergic RP ^{11}C -WAY-100635 and ^{11}C -McGN5652 in patients with parkinsonism. It has been shown that a decrease in RP uptake occurs in PD patients in the striatum structures, which correlates to the disease stage. Currently the above-mentioned RP has not received wide use and studies to this effect are sparse (Burn et al. 1995; Gunn et al. 2000; Schadrack et al. 1999).

21.6.3.3 Study of Glucose Metabolism

^{18}F -FDG is a less specific RP compared with labeled dopamine neurotransmitters, particularly as concerns early diagnosis of parkinsonism. For example, ^{18}F -FDG uptake in the lenticular nuclei may be normal or even increased in the early PD stages.

As a rule the level of regional metabolism in the projection of the globus pallidus and putamen remains unchanged also in the late pathologic stages, which is one of the main signs for differential diagnosis between PD proper and parkinsonism accompanying other neurodegenerative diseases (Fig. 21.6).

Data on metabolic changes in other brain structures detected in PD are fairly ambiguous, especially in patients with short disease duration. According to some data there are no changes whatsoever in glucose metabolism in these patients, while according to other data, increased metabolism in the motor cortex, thalami and cerebellum is observed (Eidelberg et al. 1990; Stanzhevskiy et al. 2007). Some studies indicate a decrease in glucose metabolism in the heads of caudate nuclei and anterior cingulate gyri (Brooks 1998; Stanzhevskiy et al. 2007) (Fig. 21.7).

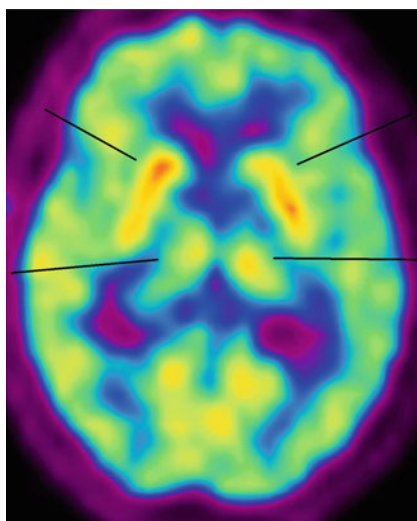


Fig. 21.6 ^{18}F -FDG PET data (axial cut) in a PD patient (second stage according to the Hoehn and Yahr Rating Scale) with a stable response to dopaminergic therapy. Some increase in glucose metabolism is observed in the thalami and lenticular nuclei (indicated with *arrows*)

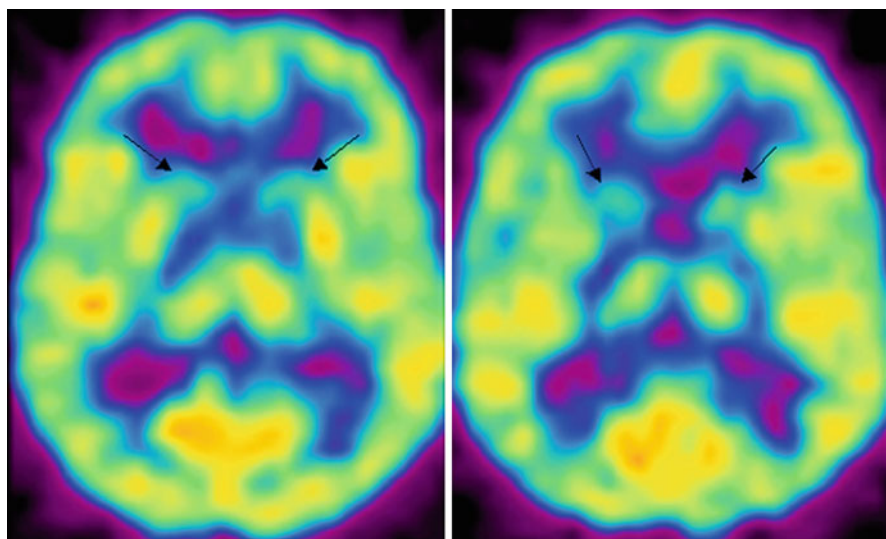
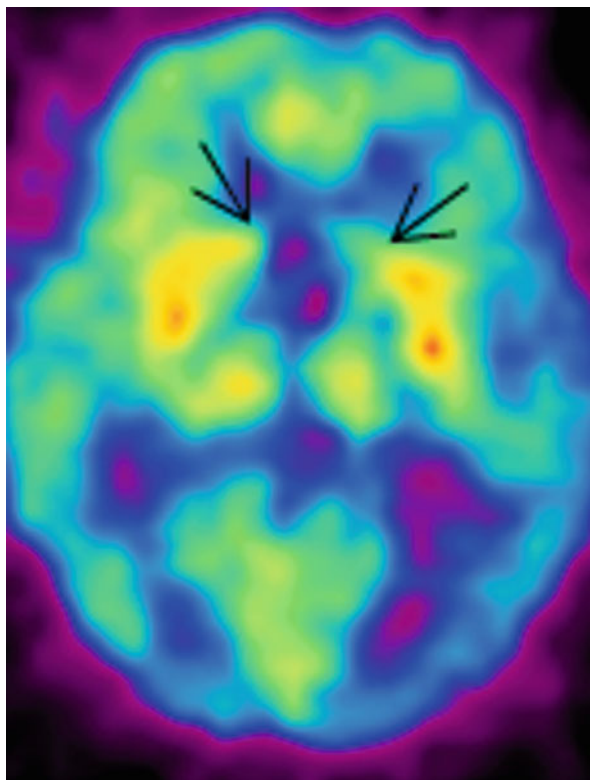


Fig. 21.7 PET data in a patient with Parkinson's disease (fourth stage of the Hoehn and Yahr scale) complicated with motor fluctuations, dementia and psychotic disorders. A diffuse inhomogeneous bilateral decrease in ^{18}F -FDG metabolism is observed in the frontal, parietal, temporal (including the hippocampus projection) cortices. Metabolism is not changed in the lenticular nuclei

In patients with long disease duration, a decrease in ^{18}F -FDG metabolism is observed in the parietal-temporal regions comparable with similar changes in Alzheimer's disease. At the same time there is no general consensus on whether decrease in glucose metabolism in the cortical structures is a specific indicator of cognitive disorders. For example, some research has shown that ^{18}F -FDG hypometabolism in the parietal and temporal cortex may be observed also in PD patients in the absence of dementia (Berding et al. 2001; Dagher et al. 2001; Ghaemi et al. 2002). However, significant hypometabolism in the mediobasal temporal lobes is known to be detected in AD in absence of a marked clinical picture of the disease. Besides that, in PD patients who take levodopa long-term, which may provoke cognitive disorders, a decrease in glucose metabolism may occur rather often or intensify in the frontal, parietal and temporal cortex and heads of the caudate nuclei; this is considered by some authors as manifestation of non-motor complications of dopaminergic therapy. In patients with late disease stages in the absence of dementia, hypometabolism is observed in the caudate nuclei and dorsolateral prefrontal cortex with normal metabolism in other brain structures including the lenticular nuclei (Fig. 21.8).

In patients with PD complicated with dementia, metabolic disturbances are characterized by diffuse hypometabolism in the cortex of both cerebral hemispheres (Bruck et al. 2001). For example, in patients with dementia and hallucinations a diffuse decrease in glucose metabolism is observed in the cortical sections of the hemispheres, including the cingulated gyri, orbitofrontal cortex and hippocampi.

Fig. 21.8 ^{18}F -FDG PET data in a patient with Parkinson's disease aggravated by motor fluctuations and dyskinesia. Hypometabolism in the heads of both nucleus caudatus (arrows) with preserved metabolism in the lenticular nuclei, thalami, cerebellum and cortex



Absence of significant changes in glucose metabolism in the lenticular nuclei should be noted in these patients (Berding et al. 2001; Wu et al. 2000). The degree of affective disorders (the sum of scores in the depression scale) in patients with cognitive disorders correlates to the degree of metabolic disturbances in the premotor and orbitofrontal cortex, which are part of the complex cortico-limbic system of the brain. In all cases of PD complicated with dementia and accompanied by visual hallucinations, the most strongly marked changes are usually observed in the occipital lobes. It should be stressed that glucose hypometabolism in the occipital region is not usually detected in patients with primary parkinsonism without dementia as well as in other neurodegenerative diseases accompanied by parkinsonism syndrome. By all appearances, these changes reflect nondopaminergic mechanisms of pathogenesis of mental disorders exceeding the limits of the nigrostriatal system.

In parkinsonism induced by multisystem neurodegenerative diseases, a sharp decrease in glucose metabolism is usually observed in the lenticular nuclei. In patients with corticobasal degeneration, these changes have an asymmetric character and are more marked in the lenticular nucleus contralateral to the affected limbs. Simultaneously, in corticobasal degeneration (CBD) patients a decrease in glucose metabolism is observed in the frontal and parietal cortex and thalami, also more significant in the structures contralateral to the affected side.

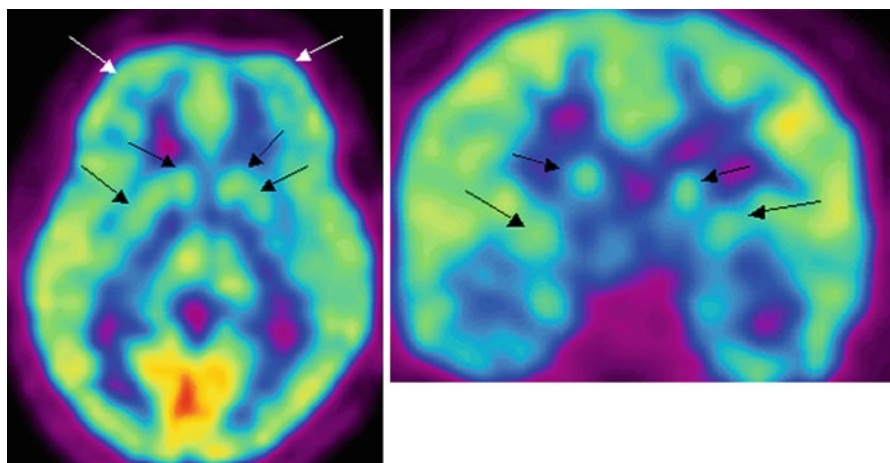


Fig. 21.9 ^{18}F -FDG PET data in a patient with PSP. Bilateral decrease in glucose metabolism in the frontal lobes, heads of caudate nuclei and in the lenticular nuclei is observed (indicated with arrows)

Progressive supranuclear palsy is characterized by hypometabolism in the deep cerebral structures combined with hypometabolism in the frontal and parietal cortex (Fig. 21.8). Metabolism in other brain cortex in progressive supranuclear palsy (PSP) is usually intact (Fig. 21.9).

In multisystem atrophy (MSA), glucose hypometabolism is observed in the striatum, especially in the striatonigral type of this disease. Hypometabolism in the cerebellum is observed virtually in all cases in olivopontocerebellar type of MSA and may be observed in patients with striatonigral MSA (Fig. 21.10). Changes in the cortex of the cerebral hemispheres are not typical of MSA (Brooks et al. 2000; Ghaemi et al. 2002; Stanzhevskiy et al. 2007). So, differential diagnosis between different nosological types of parkinsonism is based on determining the level of metabolism in the lenticular nuclei as well as in detecting glucose metabolism decrease in the cerebral cortex and basal nuclei whose localization is typical of a given form of neurodegenerative disease. Characteristic changes observed in patients with different forms of parkinsonism on examining with ^{18}F -FDG (according to our data) are shown in Tables 21.2 and 21.3 (Stanzhevskiy et al. 2007).

According to some authors, ^{18}F -FDG PET can be successfully used for assessing the efficiency of parkinsonism treatment. First of all, this regards the results of surgical therapy. For example, recent research has shown that stimulating the structures of the globus pallidus with electrodes increases metabolism in the cerebral cortex while simultaneously normalizing (decreasing) metabolism in the thalami and lenticular nuclei (Benabid et al. 2009). According to some data, bilateral stimulation of the subthalamic nuclei also induces a decrease in metabolism of the lenticular nuclei while increasing metabolism in the associative prefrontal cortex (Le Jeune et al. 2010). In another work, a decrease in glucose metabolism is reported to occur after unilateral subthalamotomy in the

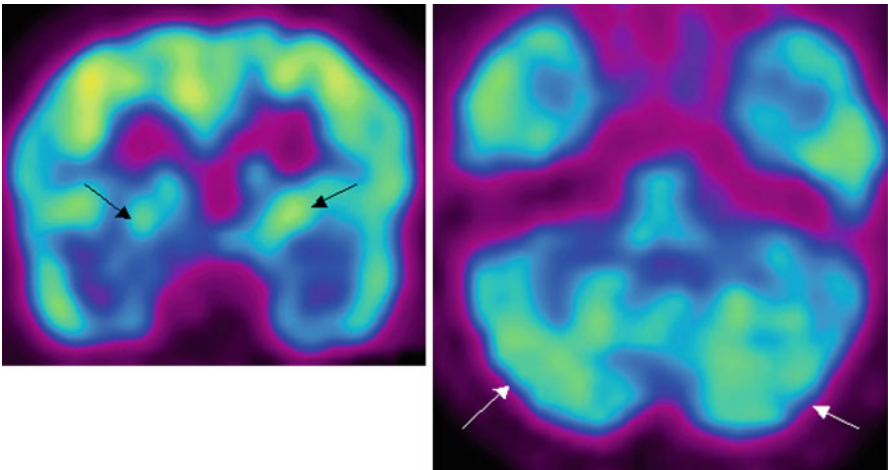


Fig. 21.10 ^{18}F -FDG PET data in a patient with MSA (the olivopontocerebellar type). Glucose hypometabolism is observed in the lenticular nuclei and cerebellum with intact metabolism in the cerebral cortex

Table 21.2 Metabolic changes detected by ^{18}F -FDG PET in patients with Parkinson’s disease

The nosologic form of parkinsonism		Uptake in the lenticular nuclei	Uptake in brain structures
PD not complicated with dementia	Early stages	Not changed or else elevated	Increase in thalami, motor cortex and cerebellum
	Late stages	Not changed	Increase in thalami, motor cortex and cerebellum Decrease in caudate nuclei, orbitofrontal and dorsolateral prefrontal cortices
PD complicated with dementia		Not changed	Increase in thalami, motor cortex and cerebellum. Diffuse decrease in metabolism in the cortical sections of the cerebral hemispheres and in limbic structures.

Table 21.3 ^{18}F -FDG PET detected metabolic changes in patients with neurodegenerative diseases complicated with parkinsonism

The nosological form of parkinsonism		Uptake in the lenticular nuclei	Uptake in brain structures
MSA	Olivopontocerebellar type	Reduced	Decrease in metabolism in the cerebellum and pons Varolii, increase in thalami
	Striatonigral type		
	Mixed type		
PSP		Reduced	Decrease in metabolism in the thalami, heads of caudate nuclei, frontal and parietal associative cortex
CBD		Reduced, more so in the nucleus contralateral to the side of lesion	Decrease in metabolism, more marked in the frontal and parietal associative cortices and thalamus contralateral to the affected limbs

projection of the globus pallidus on the side where surgical intervention was done (Brooks et al. 2000).

So the informative value of ^{18}F -FDG PET in differentially diagnosing PD and parkinsonism accompanying neurodegenerative diseases is not in fact inferior to that of examining with specific markers of dopamine neurotransmission. The advantages of ^{18}F -FDG PET over RP for assessing dopamine neurotransmission are:

- The degree of metabolic changes correlates with the severity of cognitive disorders, therefore ^{18}F -FDG PET permits assessment of the efficiency of therapy aimed at their correction.
- ^{18}F -FDG PET makes possible differential diagnosis between different kinds of neurodegenerative diseases complicated with parkinsonism.

Some of the shortcomings of ^{18}F -FDG:

- Impossibility of diagnosing PD in its early stages
- Lack of correlation between the degree of motor disorders and glucose metabolism rate
- Impossibility of assessing therapy with L-DOPA and the surgical therapy of parkinsonism (embryo mesencephalon cell or stem cell transplantation)

Thus, PET enables additional information to be obtained in order to refine PD diagnosis in difficult clinical situations. Making prognosis and determining the degree of the pathologic process. ^{11}C -SH23390 PET and ^{11}C -raclopride PET detect a simultaneous decrease in density of D_1 and D_2 receptors in the striatum in PD patients which correlates with the duration of the disease and the degree of its clinical manifestation. On average, a decrease by 5% annually in accumulation of these RPs in the striatum occurs in such patients. ^{18}F -FDG PET examinations indicate a decrease in glucose metabolism in the lenticular nuclei and heads of caudate nuclei in PD (Станжевский 2007). Besides that, in patients suffering from this disease hypometabolism in the cerebral cortex is observed, whose intensity and abundance are in direct correlation with disease duration and the severity of mental (including cognitive) disorders.

A considerable advantage of PET over other methods of examination is in the possibility of detecting preclinical forms of PD. Some authors report a decrease in density of dopamine receptors and glucose metabolism in the striatum of patients with hereditary predisposition to PD, on average 7 years before the development of its first clinical manifestations (Mazziotta et al. 1987).

Glucose metabolism and decrease in density of D_1 and D_2 receptors in the striatum may be observed in other, rarer neurodegenerative diseases belonging to the group of choreic hyperkinesias (for example, neuroacanthocytosis). However, in patients with chorea of another etiology, not associated with degenerative changes in the striatum (in Sydenham's or minor chorea, systemic lupus erythematosus, etc.) glucose metabolism rate and quantity of dopaminergic receptors in the striatum remain within the age norm or even may slightly increase compared with those in healthy people (Brooks et al. 2000).

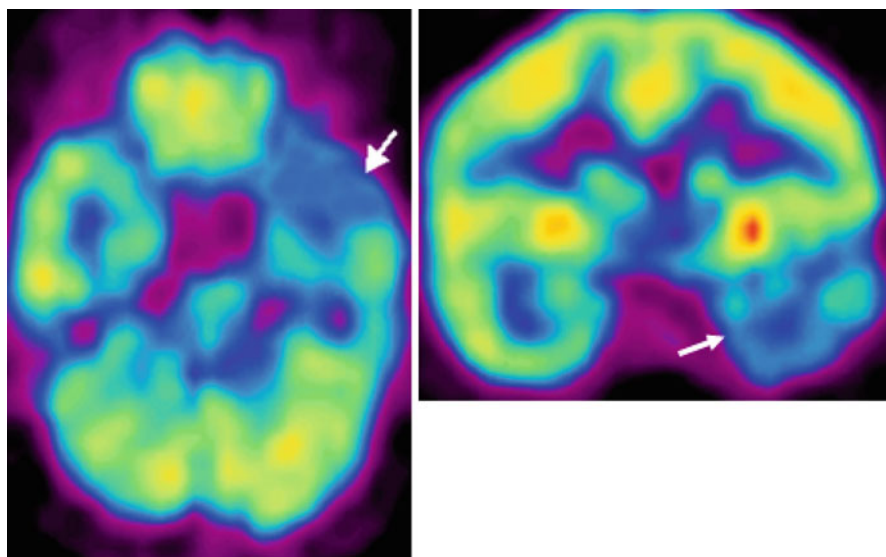


Fig. 21.11 ^{18}F -FDG PET data in a patient with the temporal lobe form of localization-related symptomatic epilepsy. Glucose hypometabolism is observed in the left temporal lobe, more marked in its medial part (indicated with arrows)

21.6.4 Epilepsy

^{18}F -FDG PET study of glucose metabolism in patients with temporal lobe epilepsy (TLE) permits to detect its decrease in 60–70% of cases.

Such a variation in assessment of sensitivity by different authors is due to particular characteristics of patient group selection and to the technical capacities of the equipment and software. Most often, a unilateral decrease in glucose metabolic activity is observed in the lateral and medial temporal lobe in temporal-lobe epilepsy (TLE) patients (Fig. 21.11).

In some patients, the expression of decrease in glucose metabolism can be bigger in the lateral temporal lobe than in the medial lobe. Much difficulty arises in the presence of bilateral hypometabolism in the temporal lobes (Fig. 21.12). In such cases, in the semiquantitative analysis of PET data moderately marked bitemporal changes may be considered as variants of the norm (Odinak et al. 2006). On the other hand, in the presence of bilateral decrease in glucose metabolism of different degrees the detected changes may be misinterpreted as unilateral. As for marked bilateral hypometabolism in the temporal lobes, it is usually rather distinctly diagnosed.

Most researchers observe that the area of neuron loss is usually inferior in volume to the region of hypometabolism which may embrace sections situated beyond the temporal lobe. For example, decrease in glucose metabolism can be detected in the

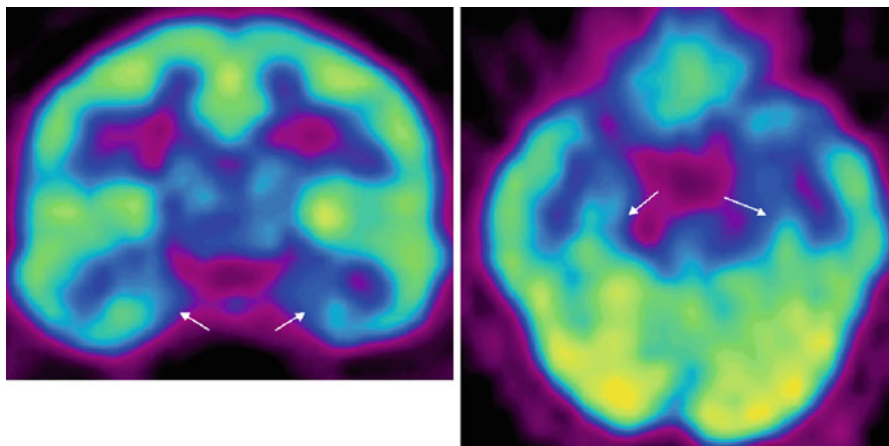


Fig. 21.12 ^{18}F -FDG PET data in a patient with the temporal lobe form of localization-related symptomatic epilepsy. Glucose hypometabolism is observed in the both mediobasal parts of temporal lobes (indicated with *arrows*), more marked on the *left side*

thalamus and basal ganglia on the side of a lesion (Tyutin and Stanzhevskiy 2002). Decrease in glucose metabolism is particularly marked in the ipsilateral dorsomedial thalamus nucleus, which has close reciprocal connections with the amygdaloid body and with other sections of the limbic system and plays an important role in the pathogenesis of TLE and in brain epileptization (Engel et al. 1997). The causes of decrease in glucose metabolism in epilepsy are not sufficiently studied so far. Hypometabolism may be due to a decrease in activity of nerve cells in the indicated brain structures because of reduced efferent impulsion from the affected hippocampus.

Overall sensitivity of ^{18}F -FDG PET in diagnosing temporal lobe epilepsy according to electroencephalography (EEG) criteria constitutes some 95%, its specificity being 66%. However, according to surgical findings, the sensitivity of the method is equal to 72%, while the specificity is 27% (Gaillard et al. 1995; Engel et al. 1990; Engel 1994; Koutroumanidis et al. 1998, 2000; Tyutin and Stanzhevskiy 2002). Probably this difference in assessment of the informative value of PET depends on the diagnostic criterion chosen due to the insufficient sensitivity and specificity of EEG. H_2^{15}O PET examination of blood flow in the temporal lobe in TLE patients in the interictal period detects an area of hypoperfusion analogous to the region of hypometabolism in ^{18}F -FDG PET. As was noted above, the area of hypometabolism in ^{18}F -FDG PET and that of hypoperfusion in H_2^{15}O PET are considerably superior in size to the zone of neuron loss, a fact which may induce misinterpretation of the obtained image (Tyutin and Stanzhevskiy 2002). For this reason, accurate localization of the epileptic focus in TLE patients necessitates both PET examinations with the mentioned RP and standard MRI in order to assess the volume of surgical intervention. H_2^{15}O PET is most often used for mapping functionally significant areas before surgical intervention in order to prevent neurologic deficiency. This mapping is of much importance in planning the resection of the temporal lobe to prevent speech disorders.

Currently much interest is attached to studying the volume of distribution and binding of benzodiazepine and opiate receptors since their disturbances have a more spatially restricted and specific character. The study of central benzodiazepine receptor (BDR) distribution in patients with TLE shows that there is a decrease in density of this distribution. Examination with ^{11}C -flumazenil (a specific marker of the GABA and BDR complex) demonstrates a decrease in BDR amount in the anterior temporal lobe without change in their density in other sections. On average a decrease in BDR binding down to 30% of its normal value is detected in TLE. Such a considerable decrease in BDR density cannot be accounted for only by neuron loss. Absence of correlation between disturbed binding of central BDR and neuron density in the epileptic focus indicates the same. Perhaps some role in reduced distribution and binding of BDR belongs to decrease in GABA synthesis and transport. A number of studies point out the high informative value of ^{11}C -flumazenil PET in diagnosing epilepsy; according to them this method permitted the detection of considerable disturbances of BDR distribution and binding in the temporal lobe in cases when high-field MRI, including volumetric analysis and T_2 -relaxometry, did not find any structural changes (Savic et al. 1993; Ryvlin et al. 1998).

The study of opiate receptors in epilepsy is not sufficiently covered in the literature. A considerable increase in opiate peptides, and connected with them delta-opiate receptors, is known to be observed in animals after the end of an epileptic fit, which suggests the participation of the endogenous opiate anticonvulsive system in the pathogenesis of epilepsy.

Study of mu-opiate receptors with use of ^{11}C -carfentanyl has shown an increase in fixation of this RP in the temporal cortex. The increase in density of mu-receptor distribution in the hippocampus and amygdaloid body has a less marked character. At the same time, it is known that mu-receptor activation in TLE may occur without general increase in number of mu-receptors (Tyutin and Stanzhevskiy 2002).

PET in Other Forms of Localization-Related and Generalized Idiopathic Epilepsy.

In most cases of extratemporal epilepsy, PET results are coordinated in agreement with MRI and EEG data. Metabolic disturbance here usually has a focal character. If metabolism decrease has a diffuse character, it usually involves the thalamus or basal ganglia. So far only solitary cases of using ^{18}F -FDG PET in diagnosing frontal lobe epilepsy (FLE) have been described (Gaillard et al. 1995; Poduri et al. 2007; Duncan 2009).

As in TLE, ^{18}F -FDG PET done in FLE patients in the interictal period detects an area of hypometabolism in the epileptic focus.

The sensitivity of ^{18}F -FDG PET in diagnosing this kind of epilepsy constitutes 56%, its sensitivity is 87%. According to other data ^{18}F -FDG PET permits detection of a regional decrease in metabolism in 60% of cases (Kuhl et al. 1980; Gaillard et al. 1995; Odinak et al. 2006). The quantitative analysis of images permits to increase the sensitivity of examination up to 96% and its specificity up to 74–78% (Cornford et al. 1998). As in case of TLE, ^{11}C -flumazenil PET has a higher sensitivity and allows more accuracy in determining the boundaries of the epileptic focus compared with ^{18}F -FDG PET. As for changes detected in occipital lobe epilepsy, they are similar to those in frontal lobe epilepsy.

The use of ^{18}F -FDG PET in diagnosing generalized idiopathic epilepsy is not completely enough covered in the literature. There are data on detecting areas of bilateral decrease in glucose metabolism in the thalami and hippocampi in patients with generalized epilepsy manifested with seizures of the kind of typical absintias (Odinak et al. 2006).

21.6.4.1 Depressions

Primary depression is most often accompanied by glucose metabolism reduction in the prefrontal cortex and heads of caudate nuclei. Secondary depression occurring in a number of diseases (PD, HC, epilepsy) is also characterized by a decrease in regional metabolism in the frontal lobes. Additionally, in these patients hypometabolism in the cingulated gyri and temporal cortex may be observed. ^{18}F -FDG PET data may have significant importance in determining the medicinal management and in monitoring therapy in order to assess its efficiency.

An important role belongs to studies on the characteristics of serotonergic neurotransmission in affective pathology (bipolar disorder and endogenous depressions). The importance of disturbances in the presynaptic link of the serotonin system in the pathophysiology of depressive states has been proved. In particular, examinations done with ^{11}C -(+)-MCN5652 have detected lowering of serotonin transporter binding, which indirectly indicates a decrease in density of 5HT-terminals or in synthesis of serotonin by neurons. These changes have been detected mainly in the thalami (Kennedy et al. 1997; Phelps 2006).

21.6.5 Anxiety Disorders

This nosologic group comprises obsessive-compulsive disorder (OCD) and Gilles de la Tourette's syndrome. OCD is characterized by persistent or recurrent obsessions (ideas, thoughts or fancies) and/or persistent compulsions (behavioral acts having a stereotypic course). Besides obsessive-compulsive symptoms, Gilles de la Tourette's syndrome is accompanied by diverse motor and vocal tics, various in duration and course. Recently data have appeared in the international literature which indicate a much greater prevalence of OCD and Tourette's syndrome (up to 2–3% of population) than considered before. Enough to say that according to some studies the number of OCD cases constitute 1–3 per 1,000 of the population and is permanently growing. In some cases the clinical manifestations of anxiety disorders prove to be resistant to conservative therapy (Shearer 2007).

In order to treat resistant forms of anxiety disorders, stereotaxic surgeries and various techniques of radiotherapy are applied. The use of stereotaxic (surgical and radiological) interventions requires rigid selection of patients as well as precise localization and adequate choice of target structures directly participating in the pathogenesis of these disorders. Using traditional methods of radiological visualization (CT or MRI) is usually little informative in determining the localization of

pathological changes in patients with anxiety disorders due to the absence of structural alterations. Therefore, in order to study the pathophysiological mechanisms of persistent therapy-resistant anxious-obsessive symptoms, to detect target structures for stereotaxic guidance as well as to evaluate the efficiency of treating anxiety disorders and obsessive disorders, PET with ^{18}F -FDG and other RPs is used.

Most ^{18}F -FDG and H_2^{15}O PET examinations indicate a disturbance in glucose metabolism or in cerebral blood flow in the limbic and striatal systems (the anterior cingulate gyri, orbitofrontal and prefrontal cortex, heads of caudate nuclei, thalami, amygdaloid bodies, Fig. 21.13) (Buchsbaum et al. 1986; Baxter et al. 1992; Braun et al. 1995, 1993; Van Laere et al. 2006; Rotge et al. 2008). The information on the nature of these changes is utterly contradictory. According to some data, cessation of therapy in patients with OCD is accompanied by an increase in glucose metabolism and cerebral blood flow rate in the prefrontal cortex, anterior cingulate gyri as well as in the thalami (Saxena and Rauch 2000; Rauch et al. 2001). According to other data, glucose hypermetabolism in the heads of caudate nuclei is observed in OCD patients before stereotaxic interventions. A decrease in regional glucose metabolism rate in this area under the effect of pathogenetically based therapy (in particular, that with antidepressants) is

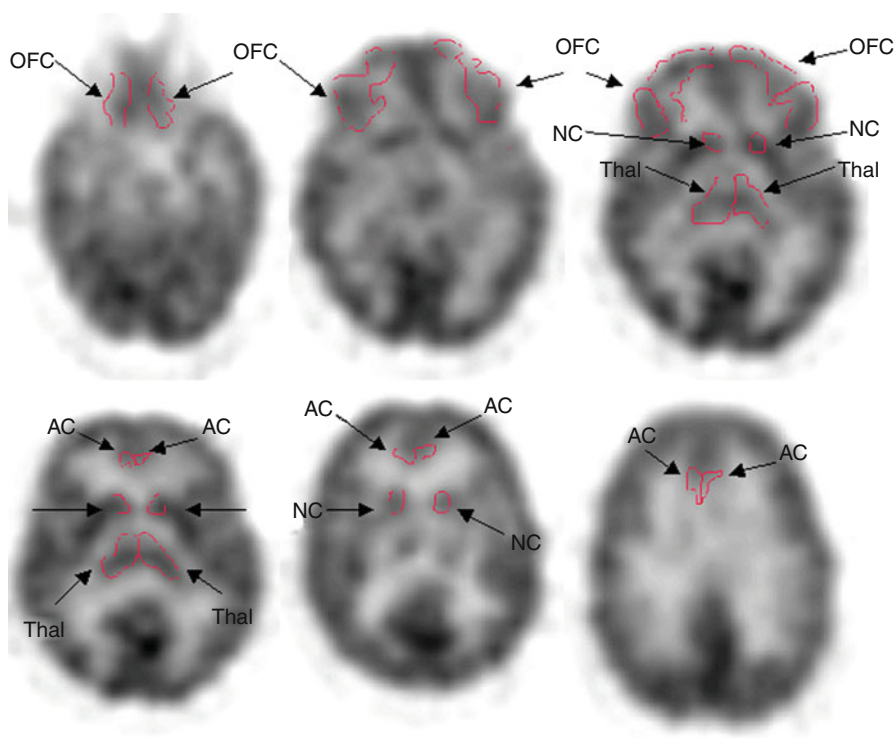


Fig. 21.13 Basic structures of the striatolimbic system, participating in the pathogenesis of anxiety disorders (OFC orbitofrontal cortex, AC anterior cingulate gyri, Thal thalami, NC heads of nuclei caudate)

accompanied by a reduction in degree of obsessive symptoms (Baxter et al. 1992). The increase in glucose metabolism in the projection of the heads of caudate nuclei was supposed to be induced by the hyperactivity of tracts going from the orbitofrontal cortex and anterior cingulate gyri to subcortical structures (basal nuclei and medial dorsal nucleus of the thalamus). At the same time, a number of studies point out a decrease in glucose metabolism in the thalami and heads of caudate nuclei in patients with anxiety disorders in acute condition (Stern 1992; Sachdev et al. 2001). After treatment (stereotaxic surgery and conservative therapy), a significant increase in glucose metabolism was observed in these patients in the indicated brain structures (Fig. 21.14) (Van Laere

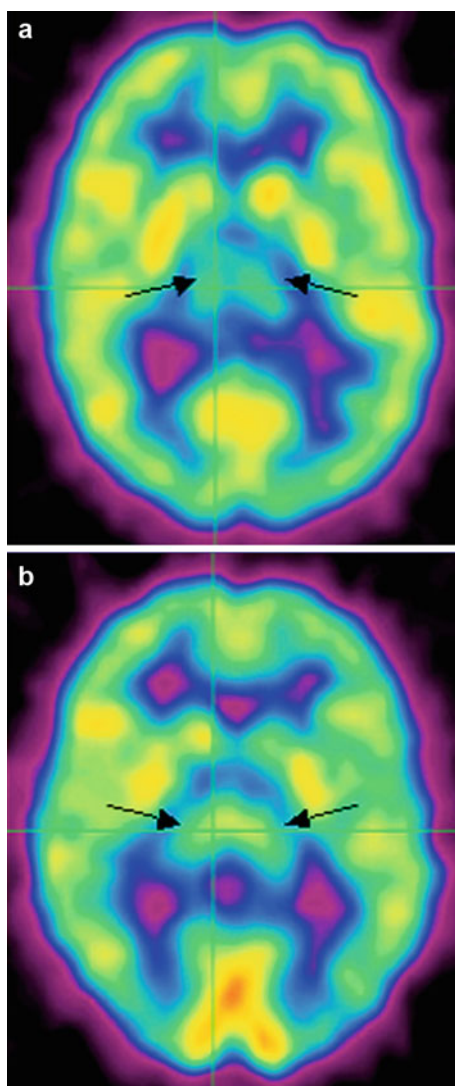


Fig. 21.14 ^{18}F -FDG data in a patient with Tourette's syndrome resistant to drug therapy. (a) PET data before treatment (Y-BOCS – 37, Spielberger-Hanin Scale-62). A significant decrease in glucose metabolism is observed in the thalami. (b) PET data after right stereotaxic thalamotomy and drug therapy (Y-BOCS – 8, Spielberger-Hanin Scale-40). A significant increase in glucose metabolism is detected in the thalami compared with preoperative examination

et al. 2006). Such a discrepancy in PET semiotics in anxiety disorders between different studies can be accounted for by the absence of unified patient selection criteria as well as those of statistical data processing. Besides, most of the studies on this problem are based on a small number of patients. It should be also stressed that there is no information in the literature as to whether there are differences in localization of metabolic disturbances between OCD and Tourette's syndrome.

It should be also noted that the issue concerning the eventual correlation between the degree of metabolic changes and clinical symptoms whose severity is assessed by means of standard tests (Yale-Brown obsessive-compulsive scale, Spielberger-Hanin anxiety scale, etc.) presently remains little studied and is covered in few publications (Perani et al. 1995; Rotge et al. 2008).

Thus, presently there is no uniform idea on the PET semiotics of anxiety disorders, dynamics of metabolic disturbances in the limbic system and striate body after treatment and on significant correlation between the regional glucose metabolism rate and the degree of clinical disease manifestations. This restricts the use of ^{18}F -FDG PET in diagnosing anxiety disorders, planning stereotaxic interventions and evaluating treatment efficiency and dictates the necessity of further advanced studies in order to solve the indicated problems.

21.6.5.1 Study of Different Neurotransmitter Systems

Recently some publications have appeared in foreign literature concerning the use of specific RPs for studying receptor systems in patients with anxiety disorders. However, when analyzed, these studies prove to give conflicting results. For example, PET studies with ^{11}C -dehydrotetraflbenazine (a specific RP for determining the activity of vesicular monoamine transporter 2 type), ^{11}C -methylphenidate (used for studying the dopamine membrane transporter) and ^{18}F -DOPA in patients with Tourette's syndrome and OCD have not detected any pathological changes in the structures of the striatal system (Saxena and Rauch 2000; Albin et al. 2009). However, there are data pointing to a decrease in density of D_1 receptors in the putamen and in the heads of caudate nuclei compared with the control group, detected by PET with [^{11}C]-SCH23390 (Saxena and Rauch 2000). Meanwhile, no correlation has been detected between the rate of decrease in number of these receptors and the degree of clinical manifestation. In another study, a decrease in ^{11}C -raclopride uptake in the basal ganglia (putamen and caudate nuclei) in OCD patients was showed after treatment with selective inhibitors of reverse serotonin uptake, which confirms the elevated activity of D_2 receptors in these pathological states and the participation of the dopaminergic system in their pathogenesis (Van Laere et al. 2006).

The results of the few studies concerning the use of specific RPs for determining the state of serotonin neurotransmission in OCD are also rather contradictory. In one of these publications it was observed that ^{11}C -DASB PET shows a decrease in activity of serotonin transporter in the mesencephalic structures and thalami. At the same time, RP uptake is in inverse correlation with the clinical severity of the disease as measured with the aid of the Yale-Brown obsessive-compulsive scale.

PET studies in OCD patients done with ^{18}F -altanserin, specific marker of serotonin-ergic receptor system (5-HT_2), have detected a decrease in density of receptors in the frontal subcortex and an increase in their number in the heads of caudate nuclei. At the same time, there was no significant change in PET imaging in these patients after treatment with selective inhibitors of reverse serotonin uptake. No correlation was either observed between the density of 5-HT_2 receptors and the degree of clinical manifestations of the disease (Saxena and Rauch 2000).

21.6.6 Schizophrenia

The first ^{18}F -FDG PET examinations in patients with schizophrenia detected a reduction in glucose metabolism in the frontal lobes (the so-called hypofrontality) compared with healthy volunteer groups. In particular, a decrease in regional glucose metabolism was observed in the prefrontal cortex (Phelps 2006).

However, over the last 15 years this phenomenon has been confirmed only in half of the studies out of more than 20 devoted to this problem. Some authors' reports indicate the asymmetry of cerebral blood flow and glucose metabolism in the form of hypermetabolism and hyperperfusion in the left temporal cortex in schizophrenia (Kotrla and Weinberger 1995; Andreasen et al. 2008). In other cases a reduction in glucose metabolism was observed in schizophrenic patients in the temporal-temporal regions and thalami (Byne et al. 2009). So the ambiguous character of results of most studies concerning glucose metabolism in schizophrenic patients is notable.

Initially the neurochemical hypothesis on the development of schizophrenia implied an excess of dopamine activity in this disease. This opinion was based on the following observation: the traditional antipsychotics such as chlorpromazine reduced the symptoms of schizophrenia by blocking D^2 receptors and interrupting dopaminergic neurotransmission. Therefore much interest was attached to dopamine metabolism and D^2 receptor density and distribution in patients with schizophrenia. In most of the studies devoted to this matter ^{11}C -raclopride and ^{11}C -N-methylspiperone were used. In spite of the large number of examinations, their results are not unambiguous. For example, in schizophrenic patients an increase in ^{11}C -N-methylspiperone uptake in the striatum is observed. Meanwhile, in the majority of studies, ^{11}C -raclopride PET does not detect an elevated RP uptake in the striatum. At the same time, there are single reports of an increase in DAA activity and in the synthesis of dopamine by neurons of the striatum in patients with schizophrenia, detected by means of ^{18}F -DOPA in comparing the obtained data with those of healthy persons (Breier et al. 1997; Kapur et al. 2000; Laruelle 1998).

Currently much interest is attached to the participation of the serotonergic system in the pathogenetic mechanisms of schizophrenia. There are isolated data on the role of disturbances in serotonin metabolism in the development of productive symptoms. Serotonin is here considered rather as a modulator of other

neurotransmitters, in particular of dopamine. In schizophrenia, changes in distribution of different subtypes of serotonin receptors in the brain matter. PET with ^{11}C -carbonyl WAY100635, ^{18}F -4-(2'-[N-(2"-pyridinyl)-p-[^{18}F]fluorobenzamido]ethyl)piperazine (^{18}F MPPF) is used in assessing the distribution of $5\text{HT}_{1\text{A}}$ receptors, while ^{18}F -setoperone and ^{18}F -altanserin are applied in studying 5HT_2 receptors (Laruelle 2000).

21.6.7 Addictive Disorders

21.6.7.1 Alcoholism

Chronic use of alcohol induces functional and morphologic abnormalities in many brain structures, in particular in the frontal cortex and cerebellum. These changes are fairly well studied in a big number of studies done by instrumental methods and with help of the analysis of autopsy material. ^{18}F -FDG PET in persons suffering from chronic alcoholism detects a decrease in glucose metabolism in the frontal cortex, particularly marked in the mediofrontal and prefrontal sections of the left hemisphere. However, due to the phenomenon of neuroplasticity, these changes and behavioral disorders associated with them may disappear after a long period of alcohol abstinence or detoxification of the organism (Adams et al. 1993; Dao-Castellana et al. 1998).

21.6.7.2 Nicotine Dependence

The participation of the dopaminergic system in the formation of nicotine dependence mediated by the cholinergic activity of nicotine has been proved. Recent research has detected significant changes in the cerebral neurochemistry in smokers compared with nonsmokers. For example, a decrease in concentration of monoamine oxydase (enzyme destroying dopamine) has been demonstrated in persons with nicotine dependence. An examination with ^{11}C -chlogiline, an acetylene amino selective inhibitor of monoamine oxidase (MAO) has detected a significant decrease in the level of MAO-A in smokers by approximately 25% in different brain structures. The activity of MAO-B measured by means of PET with ^{11}C -deprenyl in experienced smokers was lower by 40% compared with the control group. These data confirm the participation of dopamine in pathogenetic mechanisms of nicotine dependence (Fowler et al. 1996).

21.6.7.3 Cocaine Dependence

The pharmacokinetics of cocaine in the CNS has been studied in detail. This is due in particular to research done by means of PET with ^{11}C -cocaine. The maximum uptake of this RP is observed in the orbital cortex and cerebellum. Its uptake is less marked in the thalami, hippocampi and amygdaloid bodies. Cocaine is known to block the reverse uptake and transport of dopamine owing to its ability to bind with dopamine transporter. Studies with use of ^{11}C -methylphenidate

(substance similar in activity to cocaine) have shown that the level of binding of this RP with dopamine transporter directly correlates with the degree of clinical manifestations of cocaine use in drug addicts. Similar research done with ^{11}C -cocaine in drug addicts with morphological cocaine dose and under conditions of abstinence has shown a difference in ^{11}C -cocaine uptake between these groups of patients. In this study it has been demonstrated that for the signs of drug intoxication to appear more than 50% of dopamine transporter should be bound with cocaine. Cocaine-induced increase in dopamine concentration in the synaptic fissures of neurons is also confirmed in research done with ^{11}C -raclopride, whose uptake in the striatum in drug addicts is significantly lower than that in healthy people (Volkow et al. 1995, 1997).

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