

Chapter 2

The Role of Imaging in Nuclear Medicine: The Medical Perspective

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2.1 Introduction

The era of clinical nuclear medicine started already 70 years ago with the first human examination of the thyroid (Fig. 2.1). Iodine's natural affinity for the gland was used for these first examinations in patients. In 1938 the first paper on the diagnostic uses of ^{131}I in thyroid diseases in humans was published [1]. The development of this discipline has thereafter been tremendous, and still we have not seen the end of progress. Nuclear medicine has a large input in the clinical handling of patients with different diseases and is a modality to examine different physiological function in humans. It is a molecular imaging method based on emission gain by injecting the patients with a very small amount of a radioactive radiopharmaceutical or tracer. The distribution is measured with a gamma camera, a single-photon emission computed tomography (SPECT) camera or a positron emission tomography (PET) camera. In gamma and SPECT camera, radionuclides with gamma decay are used and in PET camera with positron emission.

The clinical scene in nuclear medicine today is hybrid imaging. It is the modality developing most rapidly. By hybrid imaging a combination of two different modalities is meant, most commonly SPECT and computed tomography (CT) or PET and CT, resulting in a combination of molecular/biologic and structural information displayed in a fused mode (Fig. 2.2).

Hybrid systems with a combination of PET and magnetic resonance tomography (MR) are being introduced in the clinical setting, and greater details will be given in Chap. 4. The structural part, the CT, contributes with morphologic information but also with transmission data which is used for attenuation correction of the PET or SPECT data. The strengths of CT are the spatial resolution and the contrast [2, 3]. PET and SPECT on the contrary have a relatively low spatial resolution, and the

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Fig. 2.1 An old image showing the distribution of function in a normal thyroid gland measured with ^{131}I

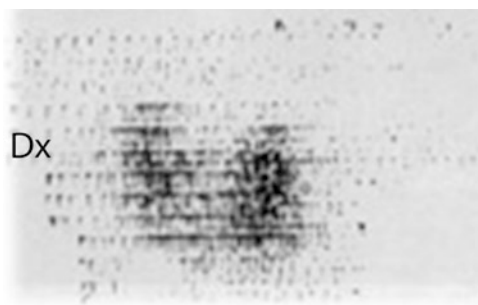
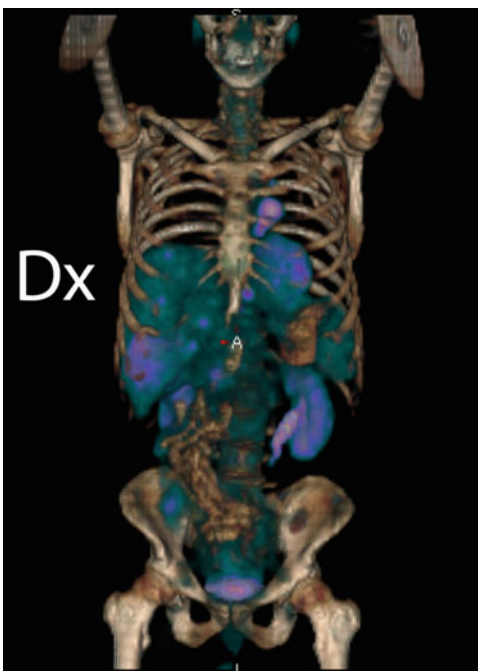


Fig. 2.2 An FDG-PET/CT 3D image of a patient with lung cancer. The skeleton is from the CT acquisition and the uptake in the liver, kidneys, bladder, heart and the lung tumour is from the PET acquisition



strength is the very high molar sensitivity giving the possibility to examine small changes in physiology [4, 5]. A comparison of different imaging modalities is shown in Table 2.1. Also gadolinium-enhanced magnetic resonance imaging (Gd-MRI), which is not based on the use of ionizing radiation, is shown for comparison.

Before an examination with radiation is done, it has to be justified. The appropriateness and the benefit versus risk have to be decided, and the examination procedure has always to be optimized. A radiopharmakon, usually consisting of a radionuclide bound to an active substance defining which function is examined, is needed. For SPECT studies the most common radionuclide is $^{99\text{m}}\text{Tc}$, a pure gamma emitter and 6 h half-life ($T_{1/2}$). For PET the working horse is ^{18}F , a positron emitter

Table 2.1 Molar sensitivity and spatial resolution for different tomographic modalities

Modality	Concentration at target	Resolution (mm)
PET	Picomolar (10^{-12})	4–6
SPECT	Nanomolar (10^{-9})	4–12
Gd-MRI	Milli-micromolar ($10^{-3/-6}$)	<0.5
CE CT	Millimolar (10^{-3})	<0.5

PET positron emission tomography, *SPECT* single-photon emission computed tomography, *Gd-MRI* gadolinium-enhanced magnetic resonance imaging, *CE CT* contrast-enhanced computed tomography

with 109 min $T_{1/2}$. The active substance can be a bone seeker, such as methyl-diphosphonate (MDP) for SPECT or fluoro-2-deoxy-2-D-glucose (FDG), which measures the metabolism in PET. The radiopharmakon or tracer can be administered to the patient in different ways, of which intravenous (iv) injection is the most common.

Nuclear medicine covers a variety of clinical questions, and it is the clinical question deciding the setup of a nuclear medicine examination. Some examples of the most common and most recent applications of nuclear medicine imaging, listed according to the imaging modality, are presented in the following sections, and some indications on future trends and need, viewed from the medical perspective, are given in the end.

2.2 Gamma Camera and SPECT Imaging

Examination of the whole skeleton with ^{99m}Tc -MDP (methyl-diphosphonate) to diagnose metastases or other bone diseases is a very common examination with conventional gamma camera (Fig. 2.3). Bone scintigraphy has been the method of choice to follow patients with oncology diseases, but imaging with different tracers in PET/CT is rapidly developing [6–8].

By using a substance measuring the regional brain blood flow (rCBF), the brain function can be measured by a SPECT or a SPECT/CT camera [9, 10]. Hexamethyl-propyleneamine oxime (HMPAO) or Neurolite is distributed in the brain in relation to the blood flow, and most of the uptake takes place during the first passage. The rationale for examination is that brain function is correlated to blood flow. The examination is used to diagnose dementia and to differ between neurodegenerative and vascular dementias (Fig. 2.4a). The same substance (HMPAO) can also be used to label white blood cells and with that substance inflammatory or infectious diagnoses can be made. This is mostly used to diagnose inflammatory bowel disorders (Fig. 2.4b). Blood flow and myocardial function can be examined with other radiopharmaceuticals. A cocaine analogue, ^{123}I -FP-CIT binding to dopaminergic neurons, is used to examine the function in striatum which is affected in parkinsonian diseases and Lewy body dementia, but not in essential tremor, making it possible to set correct diagnosis with high sensitivity and specificity (Fig. 2.5) [11–13]. If the patient is allowed to breathe an aerosol of carbon particles covered with ^{99m}Tc , the distribution of air in the lungs can be made.

Fig. 2.3 A whole body bone scintigram of a normal skeleton



This is used in combination with an iv injection of ^{99m}Tc -labelled macro-aggregates of albumin, small enough to enter the capillaries. By measuring the ventilation and blood flow distribution in the lungs, pulmonary embolism can be diagnosed. A mismatch is seen in pulmonary embolism, with activity defect in the

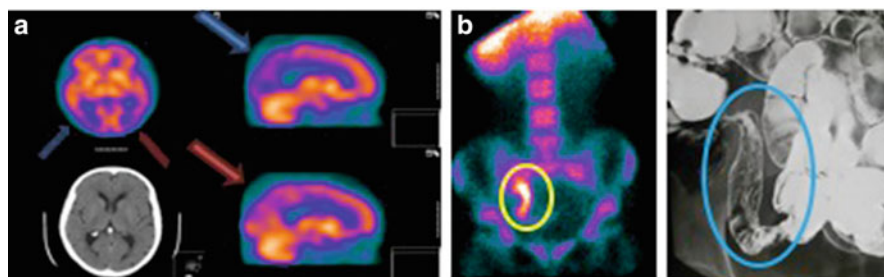


Fig. 2.4 (a) A CT and an rCBF-SPECT study with HMPAO of a patient with dementia. The blood flow is reduced in the parietal lobes bilateral (*red and blue arrows*). The CT shows no atrophy. (b) On the *left*, an intense uptake of HMPAO-labelled white blood cells is seen in the right fossa (in the *yellow circle*) in a patient under investigation of inflammatory bowel disease. The uptake is located to the bowel section with acute inflammation. On the *right*, the cobble stone appearance of the mucosa is visualized with the small bowel contrast examination

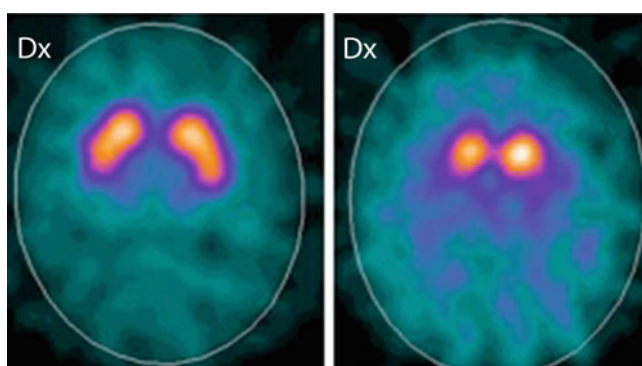


Fig. 2.5 FP-CIT-SPECT images of two patients with tremor. The one on the *left* has a normal dopamine transporter SPECT study with preserved activity in striatum bilateral and is suffering from essential tremor. The patient on the *right* has reduced activity in putamen bilateral (the lower part of striatum) and on the right nucleus caudatus consistent with a parkinsonian disease

perfusion but not in the ventilation study (Fig. 2.6). Even if CT examination of suspected pulmonary emboli is the first choice of examination, there is a clinical need of scintigraphy studies [14, 15].

2.3 PET/CT Imaging

PET/CT was introduced to the clinical practice in the beginning of 2000 [16, 17] and after that a tremendous development has been taking place. Compared to SPECT, the PET scanner has a significantly higher sensitivity and a slightly better spatial resolution (Table 2.1). Instead of using gamma emitters, positron emitters are used. A positron emitter gives away a positron from the nucleus, and since this antiparticle cannot exist, it interacts with an electron and annihilation takes place.

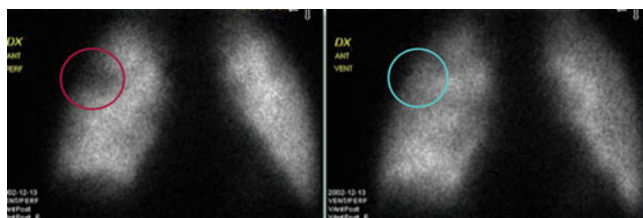


Fig. 2.6 Shows a perfusion and ventilation scintigraphy of a lung. To the *left* an image of a perfusion scintigraphy is seen. A triangular shaped region with reduced perfusion is seen in the upper lateral segment of the lung (*red circle*). To the *right* the ventilation scintigram of the same patient is shown. The ventilation in the entire lung is normal. The corresponding segment to that with reduced perfusion is delineated with a *blue circle*.

The result is that mass converts to energy, and 511 keV photons radiating almost 180° in opposite direction are produced. These 511 keV photons are measured by the PET-detectors and transformed into images, as described in Chaps. 3 and 4. The invention of PET scanning is not new, and already in the 1950s, arsenic was used to image brain tumours [18].

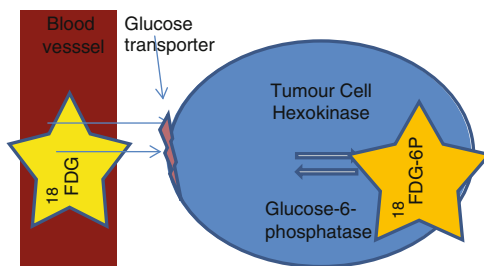
The combination of PET and CT (PET/CT) is a molecular imaging modality allowing us to visualize different biochemical pathways in cancer cells. Imaging is usually done with ^{11}C - or ^{18}F -labelled tracers. The sensitivity is high, making it possible to detect picomolar and down to nanomolar concentrations of the tracer in vivo and thus to perform imaging using non-pharmacological concentrations of the substances. This counts also for SPECT and gamma camera imaging. Oncology diseases are still the major indication for PET/CT even if the use for cardiac, brain imaging and inflammation is increasing.

Initially, the CT examination was mainly restricted to attenuation correction and anatomical mapping to facilitate the localization of the PET uptake. Today, the vast majority of PET/CT scanners are equipped with a state-of-the-art CT, and an increasing proportion of PET/CT studies are made with high-quality diagnostic CT. This true hybrid imaging sets demands on the physicians to have qualification in both radiology and nuclear medicine to evaluate the entire hybrid examination. Collaboration between a radiologist and a nuclear medicine specialist making the evaluation together is another working strategy. Furthermore, the competence of the nurses/technicians is changing, and knowledge from both radiology and nuclear medicine is needed. The clinical routine to examine patients will also change with replacement from CT to PET/CT in an increasing proportion of, for example, lung cancer patients. In summary, the development and diffusion of hybrid imaging has increased the collaboration between radiology and nuclear medicine.

2.3.1 Fluoro-2-Deoxy-2-D-Glucose

The absolute most commonly used PET tracer for imaging is FDG labelled with ^{18}F for oncologic diseases. The tracer is delivered by the blood and taken up by the tumour cells with help of glucose transporters. Inside the cell FDG is

Fig. 2.7 A schematic drawing of the FDG uptake and entrapment in tumour cells



phosphorylated by hexokinase, and the product FDG-6P does not continue in the metabolic route. It remains entrapped in the tumour cell where it can be measured by the PET scanner. Therefore, this tracer acts as a surrogate marker for metabolism, and this pathway is the one which is most frequently imaged. FDG has been in use since 1978 [19], and its use is reimbursed for most solid tumours (Fig. 2.7).

PET/CT with FDG has a high impact in clinical handling, and in 2001, a study was published showing changed clinical management of approximately a third of patients with lung cancer, colorectal cancer, melanoma and lymphoma after adding FDG-PET for staging [20]. In two publications from 2008, the impact of PET/CT on expected management of patients with cancer was evaluated based on ~23,000 PET/CT studies. These papers also concluded major changes in patient handling in approximately one-third of patients with varying oncologic diagnosis. These changes affected clinical handling for diagnosis, initial staging, restaging as well as for suspected recurrence [21, 22]. As medicines become more and more personalized, PET/CT can be of help in staging, in treatment planning and in some diagnoses also in early treatment evaluation.

2.3.2 Lung Cancer

There is a strong evidence for the use of FDG-PET/CT in initial staging for lung cancer when curative treatment is intended [23–25]. Evaluation of lymph nodes in mediastinum has the highest added value. If lymph nodes are PET negative, spread disease can be ruled out. FDG-positive nodes on the contrary are recommended to be biopsied before final staging, due to the risk of false-positive findings in inflammation. The staging with PET/CT gives major information for the treatment decision and gives also an indication of prognosis for the patient. For lung cancer, FDG-PET/CT is furthermore recommended for radiation treatment planning in order to include all active disease and to avoid radiation of for instance lung atelectasis which can be impossible to delineate with CT [24, 26].

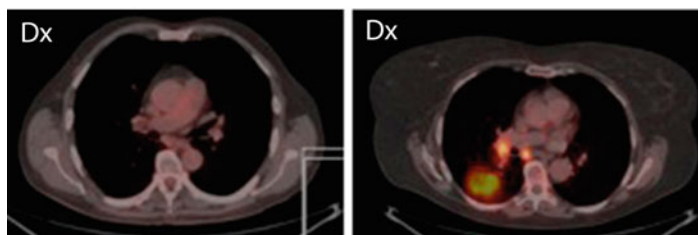


Fig. 2.8 To the *left*, an FDG-PET/CT image of a patient with lung cancer and FDG-negative border-sized lymph nodes inferior of carina. The patient underwent curatively intended therapy and is free of recurrence. To the *right*, an FDG-PET/CT image of a patient with a similar sized lung cancer and border-sized FDG-positive mediastinal lymph nodes. Curative cytoradiation was given. The patient survived 1 year after treatment and died of the disease

2.3.3 Lymphoma

FDG-PET/CT is the best modality to evaluate effect of treatment [27]. Previously only CT was used for response assessment, but recently revised Integrated International Workshop Criteria (IWC + PET) were proposed by the members of the International Harmonization Project [28]. The revised criteria combine both imaging techniques. If lymph nodes which were initially FDG avid do not show FDG uptake after treatment, the patient is considered to be in complete response, irrespective of the size of lymph nodes at CT [29]. The strength with FDG-PET/CT in lymphoma is the possibility to distinguish viable lymphomas from remnants such as necrosis or fibrosis, which are not malignant. FDG-PET/CT is also used for evaluation early in the treatment course, after two cycles of cytotoxic drugs, but more evidence is needed before the clinical role is decided [30] (Fig. 2.8). A rapid decline in FDG uptake indicates good prognosis irrespective of the CT findings. For clinical use visual assessment is used, and criteria for evaluation are published by Cheson et al. and Juweid et al. in 2008 [31, 32] (Fig. 2.9).

2.3.4 Inflammation

Beside clinical tests, structural imaging is used to diagnose vasculitis in the large arteries. It might be hard to decide correct diagnosis since half of the patients with structural findings does not have active inflammatory disease [33]. A FDG-PET/CT can help to solve the diagnostic problem in patients not on steroid treatment, and if positive, a high correlation with disease is found [34, 35] as shown in Fig. 2.10. FDG-PET/CT can also be used to diagnose infection in vessel grafts or abscesses [36, 37].

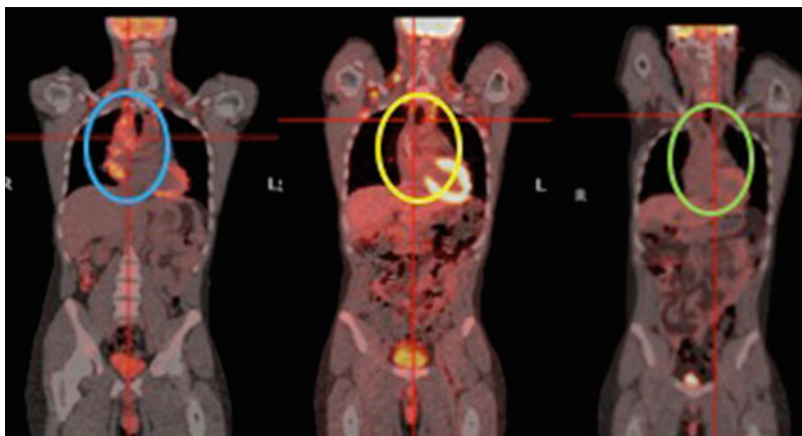


Fig. 2.9 FDG-PET/CT images of a patient with Hodgkin's disease. The image to the *left* is before treatment, the one in the middle after two treatment cycles and to the *right* after treatment is completed. Initially massive uptake in the lymphoma is seen (*blue circle*). After two circles of cytotoxic drugs, most of the lymphoma is FDG negative (*yellow circle*). After completed treatment, all lymphoma remnants are FDG negative

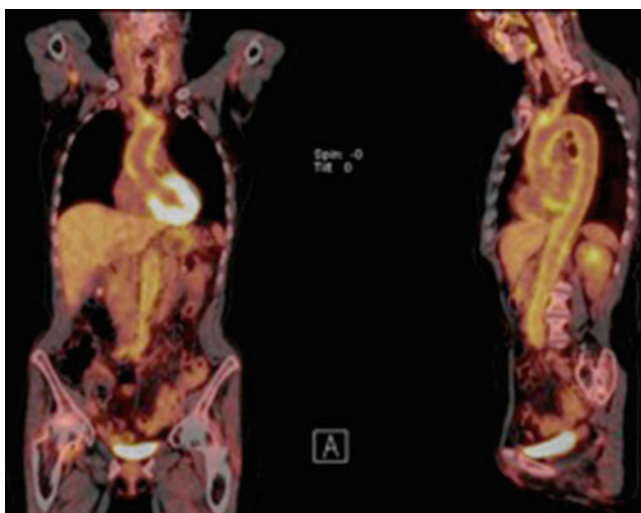


Fig. 2.10 FDG-PET/CT of a patient with a large-vessel vasculitis. The FDG uptake in the aortic wall is compatible with inflammation

2.3.5 Neurology

Several tracers are available for brain imaging [38, 39]. FDG can be used to examine the brain function and is used in dementia disorders. The metabolic activity correlates with brain neuronal function. An interesting compound is the

Pittsburgh substance, useful for imaging of dementia [40]. Other tracers can be used for imaging of the dopaminergic system, ^{11}C -raclopride for imaging of D2-receptors and DOPA to measure the dopamine production in striatum [41]. As for SPECT there is also a PET tracer to measure dopamine reuptake in striatum, ^{11}C -BCIT. The different studies of the dopamine system, pre- and postsynaptic, are mainly used for parkinsonian diseases.

2.4 Further Developments

A rapid development is still on-going, and a lot effort is put on processing of image data. This makes it possible either to decrease the acquisition time or to reduce the administered dose with remained or increased image quality. Acquisition during respiratory gating can give more detailed information for treatment planning if knowing where the tumour moves during the respiratory cycle. The respiratory gated images, 4D imaging, might also be converted into a more correct motion free image by advanced processing and morphing of image data. A goal for the development in imaging is to gain so much biological information about the disease that a personalized treatment can be decided for each patient and that each patient treatment can be individually assessed. Hybrid imaging could contribute to the goal to a large extent but information from other modalities such as MR and other biological markers are warranted to reach the goal. Most of the information is complementary not competing, and deeper knowledge of diseases is needed to take advantage of the information “hidden” in imaging.

2.5 Summary

Nuclear medicine is imaging of different physiological pathways in the body. The used radiopharmaceutical or radiotracer decides which function or molecular pathway is imaged. Introduction of PET/CT, mainly with FDG, has changed the handling in oncology substantially and made image-based personalized medicine in oncology possible [42].

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