Excursus to the World of Nuclear Medicine
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1 Introduction Nuclear medicine is based on the application of a variety of radiopharmaceuticals, either in the form of pure unsealed radionuclides or as radiolabeled compounds (tracers) for diagnostic and therapeutic purposes (endoradiotherapy).

The production of artificial radioisotopes with suitable physical properties for imaging in combination with tracers has enabled imaging a broad variety of functional (biochemical and physiological) processes in the human body and in animals. These techniques are complementing classical anatomical imaging such as radiological methods.

The latest generation of non-invasive hybrid imaging systems such as PET/CT or SPECT/CT combine emission computed tomography with transmission computed tomography (CT) to almost simultaneously collect functional and anatomic information. The information is merged into so-called fused (coregistered) images thus allowing to establish diagnoses on 3D data sets and, if desired, additionally over time (dynamic).

While endoradiotherapy is based on the emission of ionizing radiation of either alpha or beta particles from inside the body, radiotherapy (external beam radiation therapy) is a therapeutic discipline that uses gamma radiation, X-rays, electron beams, neutrons, protons, and heavy ions from outside the body or, when using encapsulated sources, from inside the body.

Radioimmunotherapy and radiochemotherapy complement the discipline of radiotherapy. All disciplines making use of ionizing radiation are regulated by the Radiation Protection Ordinance (StrlSchV) within the framework of German nuclear and radiation protection law.

2 Medical imaging methods at a glance
The various medical imaging techniques can be categorized either by the applied technique, for example:
- X-rays stored on film or digital media, computed tomography (CT) or transmission CT
- Scintigraphy, planar or in form of emission computed tomography (ECT) e.g. as utilized in single-photon emission computed tomography (SPECT) or positron emission tomography (PET)
- Sonography, medical ultrasound
- Magnetic resonance imaging (MRI)
- Endoscopy (video endoscopy)

Or by the type of images resulting from the applied techniques:
- one-dimensional (1D), two-dimensional (2D) or three-dimensional (3D)
- projection data
- cross-sectional images (axial, coronal and sagittal)
- functional images (Figure 1)
- fused images e.g. such as coregistered images of MRI and PET (Figure 2)
- static, whole-body or dynamic images.

2.1 Radiography
The projection of a volume (3D) on a planar image (2D) is the most common method, where the patient is being irradiated by X-rays from exterior.

The X-rays are absorbed by the anatomical structures they pass through in differing amounts depending on the density and composition of the material. X-rays that are not or only partially absorbed pass through the object and are recorded on X-ray sensitive film or digital media.

Objects being irradiated within the same beam direction are overlaying each other in the resulting image. It is difficult to distinguish if the contrast
seen results from the material density and subsequently higher absorption or simply the layer thicknesses.

2.2 Computer Tomography

Computer tomography is the creation of a 1D absorption profile of an object from multiple directions. Several of these absorption profiles are being used to generate a 3D structure.

The computer-based image reconstruction system is capable to determine the particular absorption for each volume element of the object (so-called voxel which corresponds to a 3D pixel) and subsequently calculate the image. For many years the filtered back projection algorithm was state of the art for the image reconstruction whereas in the recent years more and more CT systems use iterative reconstruction. [1] [2]

The calculated image is a transverse section through the object. With several rotations around the object adjacent sectional images can be created and accumulated to volume graphics that consist of several dozen or up to several hundred individual sectional images.

2.3 Scintigraphy

Imaging regional activity distribution in a scintigram is a functional-oriented examination used in nuclear medicine. The scintigram is based on the external detection of radiation from radionuclides inside the body by suitable imaging devices such as gamma cameras.

Radioactively labeled compounds (so-called tracers) are injected into the human or animal body prior to scintigraphy.

These tracers are transported, metabolized, or may be accumulated in the target organ or tissue depending on their respective metabolic characteristics.

Resulting images provide mainly physiological, pathophysiological and functional information about the scanned organism. Thus, information is provided about the spatial distribution of the activity (localization of pathological processes) and changes of activity distribution over time (functional diagnosis).

2.4 Emission computer tomography (ECT)

Where the CT (section 2.2) is based on rotation of the x-ray source and detector assembly around the object (transmission), ECT detects the radiation emitted from inside the body, i.e. the body is the source.

Both imaging methods often use iterative reconstruction for image generation (most commonly).

ECT has an obvious relevance in the field of nuclear medicine since it allows the creation of transsectional images in three orthogonal planes (transverse, coronal, sagittal) of the tracer distribution within the human body, subsequently allowing to draw conclusions about functionalities in organs, tissues, or cell structures.

2.4.1 Single-photon emission computed tomography (SPECT)

Principally this technique is based on scintigraphy (section 2.3) and is used to detect gamma radiation emitted by either radionuclides and/or tracers that have been injected intravenously.

Most often a dual-head gamma camera rotates around the body and detects the radiation from different angles, thus collecting projection data from a 360° rotation. The planar projection data are then reconstructed and converted into 2D and 3D images. Special refinements of this technique are available e.g. in form of gated SPECT acquisition where a cardiac cycle may be divided into time bins, triggered by an ECG (electrocardiogram). This technique may allow not only to assess regional myocardial perfusion but also functional parameters as regional wall motion abnormalities or calculation of the ejection fraction of the left ventricle of the heart, Figure 3.

2.4.2 Positron emission tomography (PET)

In contrast to SPECT, PET scanners require radionuclides that emit positrons (β⁺ emitters) only. PET detects the annihilation radiation resulting from the interaction of a positron with an electron inside the body. The resulting two photons are emitted at an approximate angle of 180 degrees.
to each other and with an energy of 511 keV (rest energy of an electron). These two photons from one annihilation process lead to coincidences in opposing detectors. The spatial and time-related distribution of the detected decays allows to determine the spatial distribution of the tracer.

The PET scanner contains many photon detectors arranged in a ring around the gantry. The detector rings have 30-40 detector modules, each detector module consisting of 4-8 detector blocks that are equipped with several single crystals. This results in approximately 10,000 detector crystals which are arranged in a ring (scintillation counter) and coupled to approximately 1,000 photomultipliers enabling the detection of the annihilation radiation. Coincidences between two of these detectors are registered without physical collimation (in contrast to SPECT). This advantage results in higher count rates, efficiency, resolution and ultimately image quality. Today instead of photomultipliers also technology based on semiconductors is used.

3 Nuclear Medicine

Nuclear medicine is based on the use of open radionuclides or radiopharmaceuticals (tracers) with rather short physical half-lives that emit α, β⁻, β⁺ or γ radiation.

Prior to injection they are usually coupled to substances suitable to depict organ specific processes such as perfusion, metabolism, organ functions, receptor availability and many more.

A wide range of “in-vivo” measurement methods can be used to assess the function of organs and/or organ systems, and to track the effects of treatment (e.g. chemotherapy or radiotherapy) and a range of physiological processes within the body.

Functional imaging in nuclear medicine is an interdisciplinary field which supports almost all medical disciplines. In particular, but not exclusively, these are:

- Oncology
- Urology
- Gynecology
- Otorhinolaryngology
- Cardiology
- Dermatology
- Surgery
- Endocrinology
- Neurology

3.1 Diagnostics

3.1.1 Radiopharmaceuticals in daily routine used for PET/CT

F-18-FDG (fluorodeoxyglucose)

This is the most commonly used tracer for PET. Tumor cells often have an increased affinity for glucose. Like the unlabeled physiological glucose FDG is taken up intracellularly by the glucose transporter and phosphorylated by the glucose-6-phosphatase enzym; however, then the further metabolic pathway is blocked for FDG. Therefore FDG is for some time trapped in the cell and the retention rate in the tissue is mainly related to the number and activity of the glucose transport. Similar mechanisms apply to various inflammatory cells. However, keep in mind that not all types of tumors and not all types of inflammation are FDG positive. F-18 labeled fluorodeoxyglucose (β⁺) is a positron emitter, the coincident gamma radiation of the corresponding annihilation process can be detected by the PET scanner. State-of-the-art PET scanners are always combined with a CT unit. PET and CT are consecutively acquired without the patient moving between the two examinations. This achieves the greatest possible spatial correlation between functional and structural imaging.

For most oncological indications, a hybrid scanner (PET/CT) is used for whole-body acquisitions in 3D mode. The quantitative SUV (standard uptake value) determination can objectify the degree of metabolic activity.

In the case of neurological disorders, such as some neurodegenerative diseases, the FDG brain metabolism can also be examined.
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ENVIRONMENT AND SAFETY

Ga-68-HA-DOTA-TATE for NET tumors

HA-DOTA-TATE refers to a protein molecule which resembles the body’s own hormone somatostatin.

Its special feature is that this molecule (analog to the physiological somatostatin) binds to somatostatin receptors (proteins or protein complexes) which are highly expressed on certain types of neuroendocrine tumors (NET) (e.g. gastrointestinal, pancreatic). If this molecule is labeled beforehand with a radionuclide, it is possible to visualize the tumor manifestations in the body by means of PET.

GA-DOTA-TATE is labeled with gallium-68, a positron emitter ($\beta^+\gamma$), which is used for diagnosis, staging and restaging of many NETs. In specific types of tumors most interestingly the so called theranostic concept may come into play. If the tumor burden is high and a high amount of receptor availability is documented by a preceding diagnostic Ga-68 HA-DOTA-TATE scan then replacing Ga-68 by Lu-177 may offer a specific therapeutic option to effectively treat those patients using the same principle (radiopeptide therapy). Lutetium-177, a beta emitter ($\beta^-$) with a gamma radiation component, is labeled to the same protein molecules. The therapeutic effect is based on the $\beta^-$ radiation component in the target areas (tumor manifestations). The additional gamma radiation component may be used for dosimetry and SPECT imaging following the treatment.

Ga-68-PSMA-ligand for prostate cancer

PSMA (prostate-specific membrane antigen) is a protein physiologically found on prostate cells, however which is specifically highly expressed on prostate cancer cells. Thus labeled with Ga-68, PSMA is a most interesting target suitable for PET/CT imaging in prostate cancer to determine very early recurrent tumor and metastasis. In dependency of the imaging results the further therapeutic strategy for the patients may be modified in many cases (Figure 7).

3.1.2 Radiopharmaceuticals in daily routine for SPECT/CT

Tc-99m-diphosphonate for skeletal diagnosis

Bone scintigraphy provides information on bone metabolism. Since metabolic changes usually precede
morphological findings, bone scintigraphy (Figure 8) is a very sensitive diagnostic procedure and can often detect pathological findings earlier than other examinations (e.g. conventional x-rays). In addition, bone scintigraphy as a whole-body examination allows assessment of the whole skeleton.

The radiopharmaceuticals used are Tc-99m phosphonates which are attached to the bone, depending on the extent of bone metabolism. Skeletal metastases frequently cause increased bone metabolism because of their stimulation of osteoblastic activity. Increased bone metabolism is also found in fractures, traumas, and some metabolic bone disorders.

**Tc-99m-HSA combined with Tc-99m-“gas” for lung diagnosis**

Lung diagnosis in nuclear medicine is usually performed as a combined V/P (ventilation/perfusion) examination using the SPECT/CT technique (Figure 9). For assessment of lung perfusion, a temporary microembolization of capillaries takes place after intravenous injection of small protein particles (microspheres, approx. diameter 10 to 30 μm), the size of which is slightly above the mean capillary diameter. Distribution of the radiopharmaceutical corresponds then to the regional distribution of pulmonary perfusion.

For assessment of lung ventilation, a “dry” aerosol of ultra-fine particles (size <0.01 μm) which are labeled with technetium is inhaled. Tc-99m pertechnetate is placed in a graphite crucible and evaporated in a high-purity argon atmosphere. After inhalation these radioactive labeled carbon particles are temporarily deposited in the lung alveoli (Figure 10) and thus represent pulmonary ventilation.

In this context, clearance reflects the tubular extraction rate (TER) which is calculated from the activity administered and from the activity rates measured in the serum at defined time points.

With renal function scintigraphy it is possible to determine global clearance values, partial function of the respective kidneys, identify defects in the parenchyma of the kidneys, assess the outflow and detect any extravasation from the urinary tract.

**Tc-99m-Mag3 for renal function testing**

Mag3 is a small peptide (mercaptoacetyltriglycine = “glycyl-glycylglycine”). It is extracted from the blood by the tubular cells of the kidney, secreted tubularly and almost not reabsorbed. Renal scintigraphy with Mag3 is used to detect two important parameters: a) clearance and b) partial function of both kidneys.

**Tc-99m-MIBI**

Myocardial perfusion scintigraphy (MPS) is a non-invasive examination procedure which illustrates the relative distribution of blood flow within the myocardium (left ventricle) in a 3D image (Figure 11). See also chapter 2.4.1.

As a functional imaging technique, it differs fundamentally from morphologically based imaging such as coronary angiography or coronary CT angiography (CTA) and magnetic resonance angiography (MRA) which...
image the coronary arteries directly but may not allow to draw conclusion to which extend eventual coronary artery stenosis affect local myocardial perfusion. The main clinical application for MPS is assessment of coronary heart disease. MPS is performed after intravenous injection of a radiopharmaceutical which is taken up by the cardiomyocytes in a perfusion-dependent manner. To assess the hemodynamic effects of changes in the coronary vessels on regional myocardial perfusion, SPECT images of the myocardium after injection of a radiopharmaceutical are taken after physical or drug-induced stress and at rest, and the resulting patterns of findings are interpreted.

**Sentinel lymph node (SLN)**

Sentinel lymph node diagnostics is another example applying nuclear medicine diagnostics.

It is used in the early stages of several types of tumors (e.g. breast cancer, malignant melanoma, head and neck tumors) which may spread via lymph vessels to regional and/or more distant lymph nodes.

For this procedure radioactively labeled protein particles are injected under the skin close to the primary tumor site. It is expected that lymph drainage via lymphatic channels will lead to consecutive storage of the radiopharmaceutical in the next regional lymph node. This initial first filter station is called sentinel lymph node (SLN) and has an important predictive role. The Tc-99m nanocolloid used for this type of scintigraphy is a human albumin-derivative with a half-life of 6.01 hours and an energy of 140 keV, since colloids are trapped in lymph nodes this principal is an ideal tool to detect the SLN.

Imaging is mostly performed approximately 24 hours before the planned surgical removal of the detected SLN lymph node (at that time point radiation burden for the surgical staff is below relevant borders). For imaging SPECT or SPECT/CT are the favourable techniques (Figure 12) which facilitate to localize the SLN with high diagnostic accuracy.

The approximate location of the lymph node is also marked on the skin. On the day of surgery, a hand-held gamma probe (semi-conductor or scintillation detector) is used to detect the labeled lymph node intraoperatively and then it is removed surgically.

The probe’s spatial resolution is a decisive criterion for the success of detection, i.e. the full width at half maximum (FWHM) of the resolution curve should not be greater than the actual target volume.

The real advantage of the sentinel lymph node (SLN) labeling concept is a selective surgical removal of the SLN instead of removing many lymph nodes from the axillar region with might result in lymphedema of the respective arm later.

The efficiency of the limited surgical intervention results in a reduced operating time, reduced extent of the surgery and finally the histological examination of the specific SLN probe after its removal which – as already mentioned – is a valuable predictive marker for correct assessment of the tumor stage.

### 3.2 Therapy

Nuclear medicine therapy today is mainly focused on thyroid disorders, neuroendocrine tumors, liver tumors and prostate tumors. This involves the use of open radioactive substances which are administered either orally or intravenously, which participate in specific metabolic pathways and on this way reach the target tissue in the patient’s body. Radioactive iodine-131 is used for thyroid treatment, radioactive Lutetium-177 for radioligand therapy (neuroendocrine tumors and prostate cancer) and radioactive Yttrium-90 for selective internal radiotherapy (liver tumors). Only iodine-131 is administered in pure form. As described earlier the other mentioned radionuclides are labeled with pharmaceuticals for their therapeutic use. Depending on the respective equipment, the labeling procedure may take place in the hospital’s...
dosimetry is to determine the radiative energy to the tissue during radioactive decay. The aim is to destroy the diseased tissue with its radiation. Generally before a planned treatment test are carried out to establish parameters for the dosimetric concept (intensity of accumulation in the target structure, biological half-life, etc.) Following therapy specific nuclear medicine imaging devices (SPECT/CT, PET/CT, gamma cameras) are used to document the distribution of activity in the patient’s body after therapy.

For radiation protection reasons and for observation, patients must be admitted to a nuclear medicine ward for therapy. During their stay in the hospital, regularly radioactivity measurements are performed as well as imaging of parts of the body or whole-body scans.

### 3.2.1 Dosimetry for treatment with open radioactive substances

These scintigrams are used for post-therapeutic dosimetry. The aim of dosimetry is to determine the radiation dose in the patient’s body. The dose is the amount of radiation energy transferred to the tissue and is described by the formula “dose = energy/mass” (using the unit Joule/kg = gray). The dose is primarily determined in the tumor tissue or for example in the diseased thyroid. Radioligand therapy also calculates the dose of individual organs, such as the kidneys, spleen, liver, salivary glands and bone marrow. For the dosimetry of these organs, it is necessary to determine the activity curve in them, since the transmitted radiation energy is proportional to the number of radioactive decays that have taken place in the organ. For this purpose, various images are taken during radioligand therapy using a SPECT/CT camera from GE. They include several planar scintigrams of the whole body from the ventral and dorsal aspect and a tomographic image (SPECT/CT), usually of the patient’s trunk. The evaluation software makes it possible to evaluate the planar images in such a way that the radiation pulses arriving in the camera can be determined quantitatively. The imaged organs or metastases relevant for dosimetry can be marked as regions of interest (ROI) and the pulses displayed. A calibration factor is required to calculate the activity in the organ/tumor from the pulses. The activity in the patient is known from the first whole-body scan (measuring the excretion makes it possible to deduce the activity remaining in the body), thus it is possible to calculate a calibration factor from the total number of incoming pulses in the camera. In addition, a 50 ml syringe filled with known activity is included in each whole-body image. A calibration factor can also be determined here by creating an ROI. The activity of the organs or tumor/metastases during SPECT/CT imaging can be determined with the aid of the evaluation software, as the equipment has been calibrated in advance.

A mathematical function, which approximately describes the activity curve (usually an exponential function), is then created for the activity curve, determined using the scintigrams, in the relevant organs or in the tumor tissue. The time integral of this function represents the sum of all decays that have taken place in the organ or tumor, which is important for dose calculation. To calculate the dose also requires factors which describe how much energy is transferred to the tissue per decay; the mass of the organ/tumor is also relevant. These two pieces of information can be found in the so-called S values according to RADAR (Radiation Dose Assessment Resource, related literature at ICRP and MIRD).

This information is used as the basis for dosimetry which provides an important indication as to whether target doses have been reached in tumors, metastases or in benign thyroid tissue, or which radiation dose healthy organs have been exposed to by the therapy.

#### 3.2.2 Radioiodine therapy of the thyroid

Probably the most classic and established therapy method in nuclear medicine, it has been practiced for more than 50 years and is administered in Germany 50,000 times a year. Indications are malignant disorders (thyroid cancers or their iodine-storing metastases), as well as benign disease such as autonomies, other forms of hyperthyroidism or autoimmune diseases such as Graves’ disease.

Scintigraphy using Tc-99m-PTT (pertechnetate) is used to confirm suspected diagnosis suitable for radioiodine therapy. Pertechnetate ions are actively taken up in thyroid cells in a similar way as iodide ions via the sodium iodide symporter. As a result, the pertechnetate uptake correlates to the organ’s iodine avidity. The regional uptake behavior and the extent of uptake is assessed quantitatively in the scintigram. The aims of the examination are therefore a planar functional image of the thyroid, which is always correlated with a sonogram for anatomical orientation, and the quantitative determination of pertechnetate uptake (TcTU).

This examination is followed by a radioiodine test, i.e. the imaging of a comparatively small amount of activity of iodine-131 (approx. 5 MBq). This uptake measurement (quantification of the max. iodine uptake capacity of the thyroid), which typically takes place after 5-8 days, is used to calculate the amount of I-131 to be administered during therapy in the...

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**Fig. 14.** Thyroid scintigraphy with Tc-99m-PTT - Left: Image with pinhole. A focal autonomy can be observed in the left thyroid lobe. Eventually there is also a focal autonomy of the right thyroid lobe. Right: Focal autonomy in the left thyroid lobe with almost completely suppressed paranodular tissue.
target volume. The radioiodine test is usually performed on an out-patient basis (Figure 15).

The actual radioiodine therapy takes place in one of the hospital’s controlled areas. Among other things, this is characterized by staff access restrictions. After leaving these areas, a hand-foot-clothing monitor is used to measure any contamination. Patients are admitted to hospital for at least 48 hours.

Accordingly, the therapeutic effect is based on administration of the I-131 nuclide, a β-emitter with 0.6 MeV, which is almost exclusively taken up in thyroid cells. Depending on the therapy, the activity administered is between 150-1200 MBq for benign disorders. Depending on the thyroid’s metabolism, patients may be administered additionally suppressive thyroid hormones, e.g. to suppress the uptake of I-131 in healthy thyroid tissue and to restrict the uptake only to autonomous tissue as target tissue.

In the case of malignant disorders of the thyroid, the activity administered may be many times higher in order to achieve the therapeutic goals.

4 Conclusion

Unlike any other medical discipline, nuclear medicine provides insights into many metabolic pathways illustrating various pathophysiologic concepts of the human body. It also combines a large number of medical disciplines with physics, special machine construction and computer engineering.

There are many research reports in the field of artificial intelligence where machine learning and texture analysis in fusion imaging may lead to more advanced imaging technology which, coupled with even more specific tracers, will enable even more targeted and individualized therapy in the future.

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