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Nuclear Medicine Imaging of Neuroendocrine Tumors

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Abstract

An important role is reserved for nuclear imaging techniques in the imaging of neuroendocrine tumors (NETs). Somatostatin receptor scintigraphy (SRS) with ^{111}In-DTPA-octreotide is currently the most important tracer in the diagnosis, staging and selection for peptide receptor radionuclide therapy (PRRT). In the past decade, different positron-emitting tomography (PET) tracers have been developed. The largest group is the ^{68}Gallium-labeled somatostatin analogs (^{68}Ga-SSA). Several studies have demonstrated their superiority compared to SRS in sensitivity and specificity. Furthermore, patient comfort and effective dose are favorable for ^{68}Ga-SSA. Other PET targets like β-[^{11}C]-5-hydroxy-L-tryptophan (^{11}C-5-HTP) and 6-^{18}F-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) were developed recently. For insulinomas, glucagon-like peptide-1 receptor imaging is a promising new technique. The evaluation of response after PRRT and other therapies is a challenge. Currently, the official follow-up is performed with radiological imaging techniques. The role of nuclear medicine may increase with the newest tracers for PET. In this review, the different nuclear imaging techniques and tracers for the imaging of NETs will be discussed.

Nuclear imaging techniques play a pivotal role in the diagnosis and staging of neuroendocrine tumors (NETs). Furthermore, selection of patients for peptide receptor radionuclide therapy (PRRT) can only be done by scintigraphy with radiolabeled somatostatin analogs. Besides the above-mentioned indications, nuclear imaging can play an important role in follow-up after therapy and in the evaluation of therapy response.

In general, two different imaging modalities in nuclear medicine are used to image NETs. With the gamma camera, both planar (two-dimensional) and single-photon emission computed tomography (SPECT; three-dimensional) images can be made. A

relative new image modality, the positron emission tomography (PET) camera can be used after the injection of a positron-emitting radionuclide-based tracer. The emitted positrons annihilate with a surrounding electron in the tumor or normal tissue, forming two gamma rays with an energy of 511 KeV in opposite directions. In this way, imaging with a PET camera ensures a better sensitivity and higher spatial resolution compared to the gamma camera. Currently, most PET cameras are combined with computed tomography (CT), allowing hybrid imaging in a single imaging procedure. The CT is used for attenuation correction, which improves the image quality. Furthermore, the CT can be used for anatomical correlation. This will improve the accuracy and makes it possible to distinguish between physiological and pathological activity, resulting in less false-positive findings [1, 2].

This review will focus on the different imaging modalities which nuclear medicine has to offer for the diagnosis and staging of NETs. Furthermore, selection for PRRT and the imaging options for the evaluation of therapy response will be discussed.

Imaging of Neuroendocrine Tumors

NETs are a heterogeneous group of tumors that can differ in location, function and growth. Variations in these characteristics make the presentation of a NET diverse and, therefore, the optimal diagnostic path for patients may be different. In order to perform the right type of diagnostic imaging, knowledge of the most recent World Health Organization (WHO) classification of gastroenteropancreatic NETs, as published in 2010 [3], is essential. This classification defines three tumor categories or grades, irrespective of their site of origin, based on the mitotic count (MC) and the number of cells positively staining with the proliferation marker Ki-67: low-grade (grade 1; G1) NETs with <2 mitoses/10 HPF (high-power field) and Ki-67 <3%; intermediate (grade 2; G2) NETs with 2–20 mitoses/10 HPF or Ki-67 3–20%, and high-grade (grade 3; G3) neuroendocrine carcinomas with >20 mitoses/10 HPF or Ki-67 >20%. This grading is important since there is an inverse association between grade and prognosis [4]. Besides the prognosis, the classification plays a role in the choice of imaging and/or subsequent therapy.

Somatostatin Receptor-Based Imaging

One of the characteristics of NETs is that they may express somatostatin receptors (SSTRs) on the cell surface. This receptor can be used to image tumors by using radiolabeled somatostatin analogs. In vivo visualization of somatostatin-positive tumors with radioiodine-labeled somatostatin analogs was first described in 1989 [5]. In the following years, somatostatin analogs labeled with different radionuclides were developed. These compounds have different affinities for the five subtypes of the SSTR (table 1) [6].

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Table 1. Affinity profiles (IC50) for human SSTR (hsst1–5) of a series of somatostatin analogs

	hsst1	hsst2	hsst3	hsst4	hsst5
SS-28	5.2±0.3	2.7±0.3	7.7±0.9	5.6±0.4	4.0±0.3
Octreotide	>10,000	2.0±0.7	187±55	>1,000	22±6
DTPA-octreotide	>10,000	12±2	376±84	>1,000	299±50
In-DTPA-octreotide	>10,000	22±3.6	182±13	>1,000	237±52
DOTA-TOC	>10,000	14±2.6	880±324	>1,000	393±84
Ga-DOTA-TOC	>10,000	2.5±0.5	613±140	>1,000	73±21
In-DTPA-octreotate	>10,000	1.3±0.2	>10,000	433±16	>1,000
Ga-DOTATATE	>10,000	0.2±0.04	>1,000	300±140	377±18

All values are IC50 ± SEM in nM. Modified from Reubi et al. [6].

Most radiolabeled somatostatin analogs, which are currently available for imaging, have good affinity for the subtype 2 receptor, which is most frequently expressed by NETs.

In SSTR-positive NETs, unlabeled somatostatin analogs (e.g. octreotide or lanreotide) can be used for therapy. In case patients have NETs that produce hormones, which lead to specific symptoms or syndromes (e.g. carcinoid syndrome), treatment with somatostatin analogs results in a reduction of hormonal overproduction and, therefore, relief of these symptoms. Furthermore, it can lengthen the time to tumor progression compared to placebo in patients with midgut NETs [7]. Currently, many patients with NETs are treated with somatostatin analogs. This cold octreotide can compete for binding to the SSTR with the radiolabeled somatostatin analogs. This may influence the sensitivity of the imaging and effect of PRRT. To obtain the best quality of imaging, it is therefore advised to discontinue somatostatin analogs before SSTR-based imaging and PRRT. With the proper patient preparation and imaging acquisition SSTR imaging is very helpful in the optimal staging of the patient.

[^{111}In-DTPA^{0}]octreotide

Currently, the only registered radiopharmaceutical for SSTR scintigraphy (SRS) is [^{111}In-DTPA^{0}]octreotide (OctreoScan; Covidien, Petten, The Netherlands). The SNM guideline [8] recommends an administered activity of 222 MBq and 10 μg of pentetreotide. Furthermore, SPECT(-CT) of at least the upper abdomen is mandatory for optimal imaging and staging. Due to a relative long half-life of 2.8 days, it is possible to image at 24 h and an optional 48 h after injection.

Normal tissues, such as thyroid, spleen and the pituitary gland, express SSTR. Furthermore, the liver and kidneys excrete the tracer, so accumulation of radioactivity is seen in these organs as well [9]. More specifically, approximately 2% of the administered dose leaves the body by hepatobiliary excretion. Therefore, laxatives should be considered when visualizing tumors in the abdomen. In the last decade many studies have evaluated the sensitivity and specificity of ^{111}In-DTPA-octreotide for the detection of NETs, and the results vary considerably due to variations in the size and

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location of the tumor and different acquisition protocols. A large review of 1,200 patients with gastrointestinal NETs showed a median detection rate of 89% (range 67–100%) and sensitivity of 84% (range 57–93%) [10]. Besides the presence of unlabeled somatostatin or therapeutic use of somatostatin analogs blocking the SSTR, SRS can have a negative result due to high glucocorticoid levels, which has a downregulatory effect on tumoral SSTR expression. De Bruin et al. [11] described 2 patients with a negative SRS caused by hypercortisolism due to ectopic ACTH secretion. After treatment with the glucocorticoid receptor antagonist mifepristone, the SRS pointed towards the diagnosis of an ACTH-producing bronchial carcinoid in both patients.

Furthermore, imaging of NETs with ^{111}In-DTPA-octreotide is used to select patients for PRRT. PRRT is performed with somatostatin analogs labeled with a β-emitting radionuclide such as Yttrium-90 or Lutetium-177 (e.g. [^{90}Y-DOTA^{0},Tyr^{3}] octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate). The level of accumulation in the tumor on the pretherapeutic SRS is an important prognostic factor for the prediction of tumor regression. The uptake is expressed using a semiquantitative score, comparing the accumulation in the tumor to physiological accumulation in the liver and kidneys/spleen. In general, a high accumulation in the tumor will result in a good response to therapy [12].

^{99m}Tc-Labeled Somatostatin Analogs

As an alternative to ^{111}In-DTPA-octreotide, somatostatin analogs can be labeled with ^{99m}Technetium (^{99m}Tc). Currently, the most commonly used ^{99m}Tc-labeled somatostatin analogs are ^{99m}Tc-depreotide and ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-octreotide (^{99m}Tc-EDDA/HYNIC-TOC). The latter is available under the commercial name ^{99m}Tc-Tektrotyd and most frequently used in (Eastern) Europe. The main advantage of ^{99m}Tc-labeled somatostatin analogs is the wide availability of ^{99m}Tc, which can be produced by the majority of nuclear medicine departments with the use of a ^{99m}Tc generator. This makes the production of this radionuclide relatively inexpensive. Another advantage is that the radiation burden is lower [13]. However, a disadvantage of ^{99m}Tc is the short half-life of 6 h. Because of this short half-life it is not possible to image at 24 h after injection. On the other hand, imaging can be performed on the day of the administration of the tracer and therefore disturbing bowel uptake is less of an issue. Still, it is recommended that an imaging protocol with ^{99m}Tc-EDDA/HYNIC-TOC should include acquisitions 2 and 4 h after injection, complemented with SPECT(-CT) of the upper abdomen. Using this protocol, a sensitivity of 80% and specificity of 94% could be achieved in 88 patients with NETs of the gastroenteropancreatic tract [14]. In a direct comparison between ^{111}In-DTPA-octreotide and ^{99m}Tc-EDDA/HYNIC-TOC SRS, both modalities performed similarly, with a slightly higher sensitivity for ^{99m}Tc-EDDA/HYNIC-TOC. However, the latter showed more false-positive results due to nonspecific abdominal tracer accumulation [15]. In summary, although ^{99m}Tc-EDDA/HYNIC-TOC is not widely used and only few studies have been performed with this tracer, somatostatin scintigraphy with ^{99m}Tc-EDDA/HYNIC-TOC seems a reasonable alternative for ^{111}In-DTPA-octreotide.

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Imaging with a positron-emitting radionuclide-labeled compound allows imaging with a PET camera, which results in a better image quality compared to imaging with a gamma camera including SPECT. To image NETs with PET, most somatostatin analogs are labeled with the positron emitter Gallium-68 (^{68}Ga). The most commonly used somatostatin analogs labeled with ^{68}Ga are [^{68}Ga-DOTA^{0},Tyr^{3}]octreotide (^{68}Ga-DOTATOC), [^{68}Ga-DOTA,1-nal^{3}]octreotide (^{68}Ga-DOTANOC) and [^{68}Ga-DOTA^{0},Tyr^{3}]octreotate (^{68}Ga-DOTATATE). These ^{68}Ga-labeled somatostatin analogs (^{68}Ga-SSA) all have a different affinity profile for the different subtypes of the SSTR, but have in common that each analog can bind to SSTR2. ^{68}Ga-DOTATATE has the highest affinity for SSTR2. Despite the differences in the affinity profile, the different ^{68}Ga-SSAs perform similarly with regard to sensitivity and specificity [16].

Recently, the European Association of Nuclear Medicine (EANM) published the first guideline for imaging with ^{68}Ga-labeled somatostatin analogs. In order to obtain the best imaging quality, an administered activity of at least 100 MBq and less than 50 μg of ^{68}Ga-DOTA-conjugated peptide is recommended. Image acquisition should be done at 60 min after injection [17]. A recent meta-analysis in which studies were included using various somatostatin analogs labeled mainly with ^{68}Ga with a total of 2,105 patients with NETs in the thorax and abdomen showed a pooled sensitivity of 93% and specificity of 91% [16]. It is to be expected that the ^{68}Ga-labeled somatostatin analogs will become more widely available in the near future.

Comparison between ^{68}Ga-SSA and Non-PET SRS

Several studies have compared ^{68}Ga-SSA to SRS, including ^{111}In-DTPA-octreotide, ^{111}In-DOTATOC and ^{99m}Tc-EDDA/HYNIC-TOC [18–20]. Overall, ^{68}Ga-SSA have many advantages over non-PET SRS. Firstly, as mentioned before, ^{68}Ga is a positron-emitting radionuclide, which ensures a higher spatial resolution with PET imaging. Therefore, it is not surprising that, in a direct comparison, ^{68}Ga-SSA imaging shows a significantly higher detection rate compared to non-PET SRS [18]. Especially for the detection of metastatic lesions in the bones and lungs, ^{68}Ga-SSA is superior to ^{111}In-DTPA-octreotide [19]. Due to the higher detection rate, the clinical management can change. Secondly, imaging with a ^{68}Ga-SSA is performed 60 min after injection in contrast to imaging with ^{111}In-DTPA-octreotide after 24 h. Due to the short time between injection and image acquisition it is not necessary to use laxatives when performing PET with ^{68}Ga-SSA, which is an advantage as patients often experience the use of these laxatives as burdensome. Other advantages are that ^{68}Ga-SSA is performed in 1 day, and the radiation burden for a whole-body scan is lower compared to ^{111}In-DTPA-octreotide [21]. For these reasons, the ^{68}Ga-SSA are better tolerated by the patients than ^{111}In-DTPA-octreotide [20]. Furthermore, one cost-effectiveness study comparing ^{68}Ga-DOTATOC and ^{111}In-DTPA-octreotide demonstrated that

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^{68}Ga-DOTATOC was less expensive with respect to materials and personnel costs [22]. Due to the higher sensitivity and specificity fewer additional examinations were needed.

A disadvantage of ^{68}Ga-SSA is the increase in false-positive results especially due to findings of high uptake in the pancreatic head [18, 23], which can be explained by the higher density of SSTRs in this area of the pancreas [24]. These false positive findings did not occur with ^{111}In-DTPA-octreotide, probably because of the lower sensitivity and resolution of the gamma camera. Another disadvantage remains the limited availability of ^{68}Ga-SSA. Currently, the most frequently used radiopharmaceutical for imaging of NETs is ^{111}In-DTPA-octreotide. This tracer is available in almost every nuclear medicine department and there is considerable shared experience with the interpretation of the images. Moreover, most literature is based on SRS with ^{111}In-DTPA-octreotide. Currently, the uptake on SRS can be used to assess whether a patient is eligible for PRRT. If the tumor shows less uptake than the physiological liver uptake on the SRS (grade 1 uptake), PRRT is not a suitable therapy. Such a scale is not available for ^{68}Ga-SSA and further studies are needed to translate the semiquantitative 'Krenning' score on SRS to quantitative uptake on a PET scan with ^{68}Ga-SSA.

In summary, PET imaging with ^{68}Ga-SSA performs better with regard to sensitivity and detection rate than ^{111}In-DTPA-octreotide. The discomfort for patients is lower, due to a 1-day protocol and there being no need to use laxatives. However, SRS has the advantage of better availability and larger clinical experience. It is expected that ^{68}Ga-SSA PET imaging will replace SRS in the daily practice of imaging NETs.

Other Imaging Modalities

^{123}I-Metaiodobenzylguanidine

Metaiodobenzylguanidine (MIBG) labeled with radioactive iodine (^{123}I) can be used to image NETs with planar and/or with SPECT(-CT) imaging. MIBG is structurally similar to norepinephrine and therefore utilizes the vesicular monoamine transporters and is incorporated into vesicles or neurosecretory granules in the cytoplasm of neuroendocrine cells [25]. For imaging of pheochromocytoma and paraganglioma, ^{123}I-MIBG scintigraphy has been the investigation of first choice with a high sensitivity and specificity of 87 and 99%, respectively [26]. However, new PET tracers (e.g. ^{18}F-DOPA), which will be discussed in the next paragraphs, may perform better in sensitivity and specificity, but their availability is limited. For the detection of NETs, the sensitivity of MIBG scintigraphy is lower than SRS with ^{111}In-DTPA-octreotide. In a large review, the median detection rate was 50% and the sensitivity 76% [27]. Therefore, MIBG has a limited role in the diagnosis of NETs. However, ^{123}I-MIBG scintigraphy can be used when other imaging modalities fail to detect the tumor and for the selection of therapy with ^{131}I-MIBG.

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^{18}F-Fluorodeoxyglucose

^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most frequently used PET tracer in oncology. FDG is a glucose analog that accumulates in tumor cells with a high expression of glucose transporters. The FDG undergoes phosphorylation by hexokinase and is trapped intracellularly. However, in contrast to the wide use of ^{18}F-FDG in numerous types of tumors, it has a limited role in the imaging of NETs. Poorly differentiated tumors (G3) with a high proliferative activity have an increased glucose metabolism [28]. The majority of the more differentiated tumors (G1/G2) have a normal or slightly increased glucose metabolism. For these tumors, imaging with ^{18}F-FDG should not be the first choice of imaging technique for staging. However, some G2 tumors do have an increased glucose metabolism. For these tumors, the uptake on ^{18}F-FDG PET can predict the prognosis. Overall, a high FDG uptake predicts a poorer prognosis [29, 30].

Only a few studies have compared ^{18}F-FDG to ^{68}Ga-SSA [31, 32]. Kayani et al. [31] found a significant correlation between uptake of ^{68}Ga-DOTATATE and ^{18}F-FDG and tumor grade on histology. Low-grade tumors had a higher accumulation of ^{68}Ga-DOTATATE than ^{18}F-FDG. The reverse was true in high-grade tumors. The overall sensitivity in this study for ^{68}Ga-DOTATATE was 82%, and for ^{18}F-FDG was 66%. The highest sensitivity of 92% was achieved when combining these two different PET tracers [31]. SSTR imaging and glucose metabolism imaging seem to have a complementary role [32]. Although ^{18}F-FDG-PET seems to have no additional value for the staging of patients with low-grade tumors (G1/G2), positive findings on an ^{18}F-FDG PET might define specific NET subgroups. However, it is currently not common practice to perform both imaging modalities for staging or to use this functional or metabolic information as a guidance before starting the therapy. Additional clinical studies have to be performed to gain more insight.

^{18}F- L-3,4-Dihydroxyphenylalanine

The radiopharmaceutical 6-^{18}F-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) is one of the PET tracers for imaging NETs which makes use of the capability of neuroendocrine (tumor) cells to synthesize various hormones via amine precursor uptake and decarboxylation. In the catecholamine pathway, active in many NETs, phenylalanine and intermediate products such as L-DOPA are taken up via system L large amino acid transporters. Once inside the cell, decarboxylation to dopamine takes place via the enzyme AADC (aromatic amino acid decarboxylase). Dopamine is then transported into intracellular storage vesicles through the vesicular monoamine transporter. From these vesicles, the resulting end products can be released in the extracellular environment.

Nowadays, more and more PET centers are capable of producing ^{18}F-DOPA, and it is commercially available in several European countries. Usually, images are made 60–90 min after injection, although earlier images are advocated for some indications [33, 34]. Physiological variants and pitfalls have been described [34, 35]. Practices differ regarding premedicating patients with carbidopa for NET imaging. Carbidopa is

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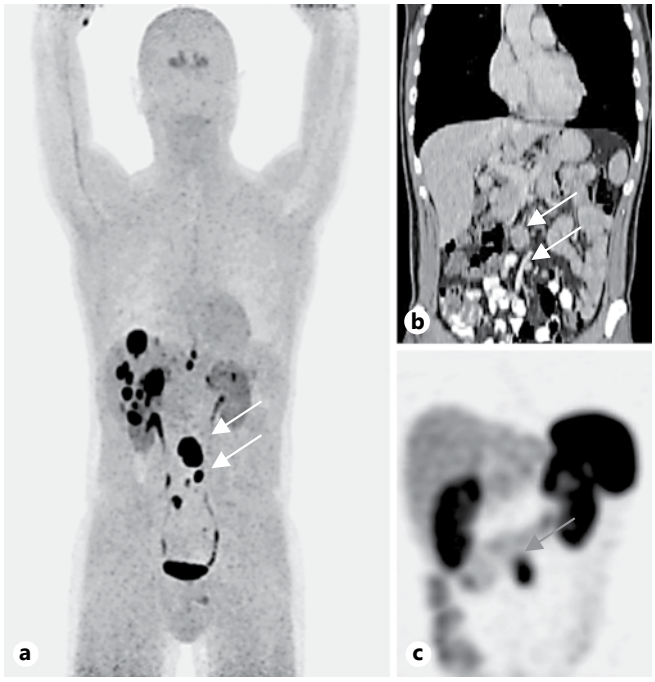

Fig. 1. A patient with liver and mesenteric lymph node metastases from a small bowel G1 NET. **a** Maximum intensity projection of whole-body ^{18}F-DOPA PET showing multiple liver lesions and metastases in the mesenterium. Physiologic uptake is seen in the striata. Physiological excretion is via the kidneys and ureters to the bladder. **b** Abdominal CT showing large and smaller (white arrows) malignant mesenteric lymph nodes. **c** On the ^{111}In-DTPA-octreotide SPECT scan 24 h after injection only the large mesenteric lymph node could be visualized (gray arrow).

an inhibitor of AADC, and it prevents early decarboxylation of ^{18}F-DOPA to ^{18}F-dopamine outside the brain. This results in decreased renal excretion and increased ^{18}F-DOPA uptake in NET cells, thus increasing image quality and sensitivity [36, 37]. However, carbidopa pretreatment is not recommended for the evaluation of pancreatic pathology, such as congenital hyperinsulinism/nesidioblastosis or insulinomas [38, 39].

Most studies with ^{18}F-DOPA PET have been performed for diagnosing and the (re-)staging of NET patients. Its superior role has been established in the following, more common subtypes of NETs: well-differentiated NETs of midgut origin, pheochromocytoma/paraganglioma and medullary thyroid carcinoma. In these NET types, ^{18}F-DOPA PET/CT can serve as the initial imaging technique, provided that it is available [40]. In well-differentiated NETs of midgut origin, overall (n = 76 patients) patient- and lesion-based sensitivity for ^{18}F-DOPA is 89 and 97%. This is significantly higher when compared to SRS with ^{111}In-DTPA-octreotide (80 and 49%, respectively; fig. 1), and is equal compared to CT/MRI (89% patient based) or higher (65% lesion based) [40]. Furthermore, in these patients, the extension of ^{18}F-DOPA uptake on the whole body PET scan reflects the total tumor load, and was correlated with various urinary and plasma hormonal products, but not with serum chromogranin A [41]. Thus far, patient series directly comparing ^{18}F-DOPA and ^{68}Ga-SSA in NET patients are small. Preliminary results suggest that they perform equally well [40]. An example is given in figure 2.

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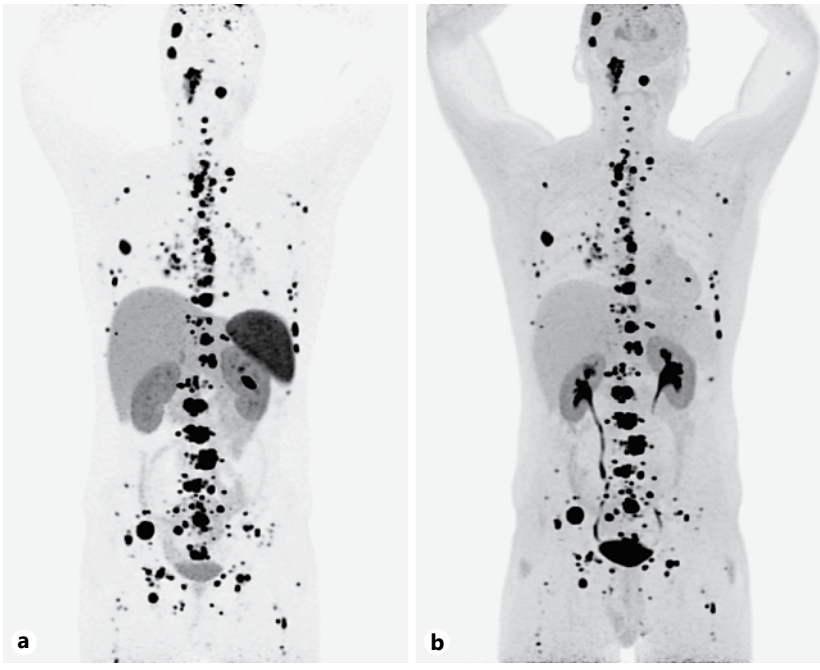

Fig. 2. A patient with paraganglioma with widespread (bone) metastases. **a** Maximum intensity projection (MIP) of whole-body ^{68}Ga-DOTATATE PET. **b** MIP of whole-body ^{18}F-DOPA PET. Note the similarity of uptake of ^{68}Ga-DOTATATE and ^{18}F-DOPA in the lesions. Only some lesions take up ^{68}Ga-DOTATATE (e.g. axillary regions), but this might be due to PD (the acquisition was 6 months after the ^{18}F-DOPA PET).

There are differences of opinion as to whether or not ^{18}F-DOPA should be advised as a first-choice functional imaging technique in patients with pancreatic NETs. Other functional imaging techniques such as ^{111}In-DTPA-ocetreotide SRS, ^{68}Ga-SSA PET or ^{11}C-5-HTP PET may be considered as well [35, 39, 40, 42].

β-[^{11}C]-5-Hydroxy-L-Tryptophan

PET imaging with β-[^{11}C]-5-hydroxy-L-tryptophan (^{11}C-5-HTP) PET can visualize the serotonin pathway, which is active in many NETs. The precursors tryptophan and 5-HTP are taken up via the L-amino acid transporter, and subsequently decarboxylated by aromatic L-amino acid decarboxylase (DOPA decarboxylase, tryptophan decarboxylase) ADCC. This results in serotonin, which is then also stored in vesicles through the vesicular monoamine transporter. When released into the extracellular environment, serotonin is thereafter degraded and eventually excreted as urinary 5-hydroxyindole acetic acid (5-HIAA).

^{11}C-5-HTP is produced in only a few centers worldwide, since the tracer synthesis is very complex. It is advised for the pretreatment of patients with carbidopa [43]. Whole-body imaging usually starts 10–20 min after injection of the tracer. Based on the limited studies that have been published, it can be concluded that ^{11}C-5-HTP is a

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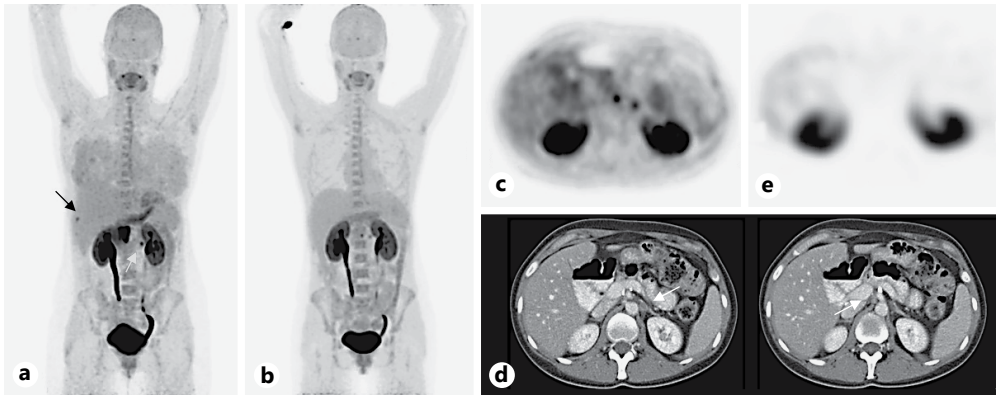

Fig. 3. A patient with insulinoma G2 of the pancreas, pT3N1M1. **a** Maximum intensity projection of whole-body ^{11}C-5-HTP PET before surgery. The primary tumor is seen in the head of the pancreas. Also, a liver metastasis (black arrow) and a locoregional lymph node metastasis were detected. All were surgically removed. Physiological uptake is seen in salivary and mammary glands, mucosa of the esophagus and bone marrow. Physiological excretion is via the kidneys and ureters to the bladder. **b** Six months later, during follow-up with ^{11}C-5-HTP PET and a diagnostic CT of the abdomen, two small new locoregional metastatic lymph nodes were detected. **c** Transverse slices of ^{11}C-5-HTP PET/CT showing the two new lesions, para-aortic right and left sided. **d** Transverse slices of the diagnostic CT of the abdomen (venous phase), also showing the two new lymph node metastases. **e** A follow-up ^{111}In-DTPA-octreotide SPECT scan (transverse slice) failed to detect these small metastases.

universal NET tracer for all tumors arising from the fore- to hindgut [44, 45]. It has been suggested that ^{11}C-5-HTP performs better compared to ^{18}F-DOPA, especially in foregut (e.g. bronchial) NETs, but this needs further confirmation [33]. In a recent study, Orlefors et al. [46] reported for ^{11}C-5-HTP PET a sensitivity of 83% and specificity of 100% in 38 patients with abdominal NETs, confirmed by surgery and histopathology results. An example of a ^{11}C-5-HTP PET is given in figure 3.

Based on a study by Koopmans et al. [47], it was concluded that ^{11}C-5-HTP PET outperforms ^{18}F-DOPA PET both in a patient- and a tumor lesion-based analysis in patients with predominantly advanced pancreatic islet cell tumors. However, as stated earlier, there are different opinions regarding the choice for a functional imaging PET tracer in this patient group. Not only for pancreatic NETs, but also for other (subsets) of NETs, further research is needed to define more precisely the role of both metabolic pathway tracers, ^{18}F-DOPA and ^{11}C-5-HTP, also in relation to other new functional PET tracers that are currently being developed or are already in use.

Glucagon-Like Peptide-1 Receptor

A rare type of NET is the insulinoma. The great majority (more than 90%) of insulinomas are benign, but they can be life threatening due to increased excretion of insulin and induction of episodes of hypoglycemia. Approximately 10% of the insulinomas are multiple, mainly in genetic polyendocrine syndromes. Insulinomas are the

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most common cause of endogenous hyperinsulinemic hypoglycemia in adults. Virtually all insulinomas are located in the pancreas, but 10–27% remain undetected even after surgery [48]. Preoperative localization is therefore essential to facilitate and optimize surgery. The sensitivity of ^{111}In-DTPA-octreotide for detection of insulinomas is only 50–60% [49]. Because of this relatively poor sensitivity, other imaging targets such as the glucagon-like peptide-1 receptor (GLP-1R) have been recently developed. GLP-1R is expressed at very high density in almost all benign insulinomas [50]. The first studies with GLP-1R agonists demonstrated very promising results [51, 52] with a high detection rate compared to conventional imaging. However, these agonists are not commercially available. Unlike benign insulinoma, malignant insulinomas often lack GLP1-R. In contrast, the malignant insulinomas often express SSTR type 2, which can be visualized by SRS [53].

Imaging Response after Therapy

Adequate assessment of response after therapy is important in NET patients. Not only will it predict the prognosis of the patient, but it will also influence the decision to continue the current therapy or to switch to other alternative therapies. The most frequently used assessment method during follow-up is the response evaluation criteria in solid tumors (RECIST). This assessment is based on the number and size of the lesions measured on CT and, in certain situations, MRI or chest X-ray. The latest guideline version was published in 2009 [54]. A partial response (PR) is defined as a decrease of at least 30% in the sum of the diameters of target lesions. Progressive disease (PD) is defined as a 20% increase in the sum of the diameters of target lesions. Stable disease is every change that is not sufficient for PD or PR. Another response evaluation assessment method is the Southwest Oncology Group (SWOG) solid tumor response criteria. The SWOG criteria use a slightly different method for tumor measuring and different definitions for PD and PR. In a direct comparison between the RECIST and SWOG criteria in patients treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate, there were no significant differences in the evaluation of responses [55]. In general, NETs are slow-growing tumors and most therapies do not lead to shrinkage of tumors, but stable disease instead. Therefore, the RECIST criteria using morphological volume characteristics may not be the ideal response criteria for relatively slow-growing NETs (i.e. G1/G2 tumors). Different groups have tried to develop new criteria for response evaluation based on nuclear imaging techniques. A small study with 4 patients found a more appropriate evaluation with the tumor-to-nontumor ratio (T/nT) on SRS with ^{99m}Tc-EDDA/HYNIC-TOC in combination with volume and attenuation changes on CT [56]. With the newest ^{68}Ga-SSA, it is easier to measure the change in standardized uptake value (SUV). Haug et al. [57] measured the tumor-to-spleen SUV ratio and maximum SUV ratio at baseline and 3 months after the first cycle of PRRT. They found a significant correlation with improvement in clinical symptoms.

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Moreover, the decrease in tumor uptake predicted a longer time to progression. On the other hand, Gabriel et al. [58] found that an SUV analysis of individual lesions did not have an additional value in the prediction of individual responses to therapy compared with conventional anatomical imaging with CT. It is clear that further investigation is needed. A disadvantage of somatostatin-based imaging is that NETs may lose their receptors and become negative on these images. Therefore, it would be very interesting to measure the response with metabolic tracers like ^{18}F-DOPA or ^{11}C-5-HTP, which demonstrate metabolism within the tumor rather than expression of receptors. Unfortunately, there are so far no data available on the use of these tracers for response evaluation, but this type of response evaluation will become paramount within the next decade.

Conclusion

The initial diagnosis of NETs is made with radiological and histological methods. Nuclear imaging techniques are essential to estimate the total disease burden. Currently, the gold standard for the imaging of NETs is SRS with ^{111}In-DTPA-octreotide. It is almost certain that in the near future this will be replaced by ^{68}Ga-SSA PET imaging. ^{18}F-FDG PET has a limited role in the imaging of NETs, but may play a role in predicting the prognosis in G2/G3 tumor patients. ^{11}C-5-HTP and ^{18}F-DOPA PET show very promising results but are more difficult to produce and/or not widely available. ^{18}F-DOPA is commercially available in several European countries and its use may increase in the coming years. Besides, ^{18}F-DOPA has broader imaging applications than only NETs. Currently, selection for PRRT is based on SRS; further research needs to be done to translate the uptake on SRS to accumulation in the tumor on ^{68}Ga-SSA imaging. Subsequently, changes in tumor accumulation after therapy using metabolic tracers can have an additional value to the existing response criteria based on CT/MRI.

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