Abdominal Radiology (2022) 47:4058–4072
https://doi.org/10.1007/s00261-022-03516-2

SPECIAL SECTION: NEUROENDOCRINE NEOPLASMS

PET/CT and PET/MRI in neuroendocrine neoplasms

Naveen Rajamohan[1] · Hala Khasawneh[1] · Aparna Singh[1] · Garima Suman[1] · Geoffrey B. Johnson[1] · Shounak Majumder[2] · Thorvardur R. Halfdanarson[3] · Ajit H. Goenka[1]

Received: 12 February 2022 / Revised: 25 March 2022 / Accepted: 28 March 2022 / Published online: 15 April 2022

Abstract

Advanced molecular imaging has come to play an integral role in the management of gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs). Somatostatin receptor (SSTR) PET has now emerged as the reference standard for the evaluation of NENs and is particularly critical in the context of peptide receptor radionuclide therapy (PRRT) eligibility. SSTR PET/MRI with liver-specific contrast agent has a strong potential for one-stop-shop multiparametric evaluation of GEP-NENs. ^{18}F-FDG is a complementary radiotracer to SSTR, especially in the context of high-grade neuroendocrine neoplasms. Knowledge gaps in quantitative evaluation of molecular imaging studies and their role in assessment of response to PRRT and combination therapies are active research areas. Novel radiotracers have the potential to overcome existing limitations in the molecular imaging of GEP-NENs. The purpose of this article is to provide an overview of the current trends, pitfalls, and recent advancements of molecular imaging for GEP-NENs.

Keywords Positron emission tomography-computed tomography · Magnetic resonance imaging · Neuroendocrine tumors · Gallium radioisotopes · Fluorodeoxyglucose F18

Introduction

Around two-thirds of all neuroendocrine neoplasms (NENs) originate in the gastrointestinal system [1, 2]. Gastro-entero-pancreatic (GEP) NENs can occur at any age; however, the incidence exceeds 10 per 100,000 population between 70 and 84 years of age [3, 4]. There has been a steady rise in the incidence of GEP-NENs over the last decade, likely due to increased awareness and the wider use of advanced cross-sectional imaging [5–7]. Most GEP-NENs are non-functional and remain clinically indolent, but metastases are common and often the source of symptoms [8]. Conversely, a subset of GEP-NENs are functional and present at earlier stages due to clinical manifestations induced by hypersecretion of various bioactive hormones, which can be debilitating. The majority of GEP-NENs are sporadic. However, a small subset of NENs can arise in the context of syndromes such as Multiple Endocrine Neoplasia type 1 (MEN1), Von Hippel Lindau syndrome (VHL), Neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC) [9]. Despite the high prevalence of metastatic disease, GEP-NENs tend to have a good prognosis with a mean survival of around seven years [10]. However, the prognosis substantially varies with the site of the primary tumor. For instance, the average 5-year survival is around 54% for pancreatic NENs and nearly 100% for gastric NENs [10, 11].

The 2019 WHO system classifies NENs based on their mitotic activity and Ki-67 proliferation index (Table 1) [12, 13]. High-grade (G3) NENs are now stratified into two histologically and genetically distinct groups, i.e., the well-differentiated and poorly differentiated groups. The latter are now termed neuroendocrine carcinomas (NECs) [12]. There have been significant recent advances in the diagnosis, staging, and multidisciplinary treatment of NENs. One of these is the molecular imaging of NENs with somatostatin receptor (SSTR)-targeted PET, which has largely supplanted conventional gamma SSTR scintigraphy and single-photon emission-computed tomography (SPECT). The purpose of this article is to provide an overview of the current trends,

✉ Ajit H. Goenka
goenka.ajit@mayo.edu

[1] Department of Radiology, Mayo Clinic, 200 First Street SW, Charlton 1, Rochester, MN 55905, USA

[2] Department of Gastroenterology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

[3] Department of Medical Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Table 1 Grading system for NENs (Based on WHO 2019 and AJCC 2017)

	Histologic differentiation	Grade	Ki-67 index^	Mitotic index Φ
G1 NEN	Well-differentiated tumors	Low	< 3%	< 2
G2 NEN	Well-differentiated tumors	Intermediate	3–20%	2–20
G3 NEN	Well-differentiated tumors	High	21–55%	> 20
NEC- Small and Large cell	Poorly differentiated tumors (Small cell or Large cell)	High	> 21%, (usually > 55%)	> 20
MiNEN	Well or Poorly differentiated	Variable	Variable	Variable

^ Percentage of cells with a positive reaction on immunocytochemistry with MIB1 antibody

Φ Number of mitotic figures within ten high power fields

NEN Neuroendocrine neoplasm, *WHO* World Health Organization, *AJCC* American Joint Committee on Cancer, *NEC* Neuroendocrine carcinoma, *MiNEN* Mixed neuroendocrine–non-neuroendocrine neoplasm

pitfalls, and recent advancements of molecular imaging for GEP-NENs.

Molecular imaging of GEP-NENs

Successful targeted molecular imaging of GEP-NENs is dependent upon the overexpression of SSTRs by these neoplasms. There are six subtypes of SSTRs (1, 2A, 2B, 3, 4, & 5). Of these, subtype 2A has the highest expression in GEP-NENs, particularly low-grade (G1 and G2) NENs [14]. ^{111}Indium (^{111}In)-diethylene-triamine-penta-acetic acid (DTPA)-pentetreotide had been the traditional radiopharmaceutical for planar somatostatin receptor scintigraphy (SRS) and SPECT imaging of NENs. However, it had a high false-negative rate in organs that show high physiological uptake (e.g., liver), low spatial resolution, required long scan times, resulted in relatively high radiation dose to the patient, and orders of magnitude lower affinity for SSTRs compared to SSTR-targeted PET radiotracers. Therefore, it has been largely replaced by SSTR PET, which has become the current reference standard for molecular imaging of GEP-NENs.

In current clinical practice, SSTR PET is performed with ^{68}Gallium (^{68}Ga) or ^{64}Copper (^{64}Cu)-tagged peptides such as -TATE (Tyr3-octreotate), -NOC (NaI3-octreotide), and -TOC (TyI3-octreotide), which are chelated with DOTA (1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid) to produce ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC, and ^{68}Ga-DOTATOC, respectively. Although there are minimal differences in the SSTR affinity of these agents, there is no clear superiority of one over the other in clinical practice. ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC are approved by the US Food and Drug Administration (FDA).

Compared to SRS, SSTR PET has significantly higher sensitivity for the detection of metastatic NENs, which translates to a substantial impact on clinical management [15–17]. The superior sensitivity is due to multiple factors such as the higher affinity of PET radiopharmaceuticals for SSTRs coupled with the higher spatial resolution and physical sensitivity of PET cameras. Thus, SSTR PET can detect more and smaller lesions, including those with low-to-moderate SSTR expression (Fig. 1). PET also offers faster throughput and a shorter overall scan time (a few hours for SSTR PET versus 2–3 days for SRS), the ability to quantify radiotracer uptake through standardized uptake values (SUVs), and lower effective radiation doses [17]. Therefore, recent guidelines recommend that SSTR PET replaces SRS for all clinical indications used previously (Table 2) [18].

^{64}Cu-labeled DOTATATE is another PET radiotracer that was more recently approved by the FDA. The longer physical half-life of ^{64}Cu, 12.7 h, compared to 68-min for ^{68}Ga, can be an advantage because it allows for its central production and transportation to peripheral facilities that lack access to ^{68}Ga. Second, it has a shorter positron range in tissue (0.6 mm versus 3.5 mm for ^{68}Ga) and lower physiologic uptake in the liver. These properties have the potential to provide superior imaging quality, especially at delayed time points (3–24 h after injection). One comparative study found higher detection of true positive lesions with ^{64}Cu-DOTATATE than ^{68}Ga-DOTATOC, especially in the liver. However, a patient-based analysis revealed no significant difference [19]. Second, a dual-time point imaging study of ^{64}Cu-DOTATATE showed similar accuracy for 1 and 3 h time points. ^{64}Cu-DOTATATE is also prone to in vivo demetallation and transchelation, which may reduce image quality [20]. Finally, compared to ^{68}Ga-DOTATATE, ^{64}Cu-DOTATATE emits fewer positrons per annihilation event and emits beta emissions, which contribute to increased patient radiation dose and limit the permissible dose to the patient. Thus, to achieve image quality comparable to ^{68}Ga-DOTATATE PET with an equivalent effective dose, the scan time needs to be increased for ^{64}Cu-DOTATATE PET. New sarcophagine-based chelators such as ^{64}Cu-SARTATE have shown high retention in the tumor at delayed time point imaging with progressive clearance from the liver and have the potential to provide better results than ^{64}Cu-DOTATATE [21].

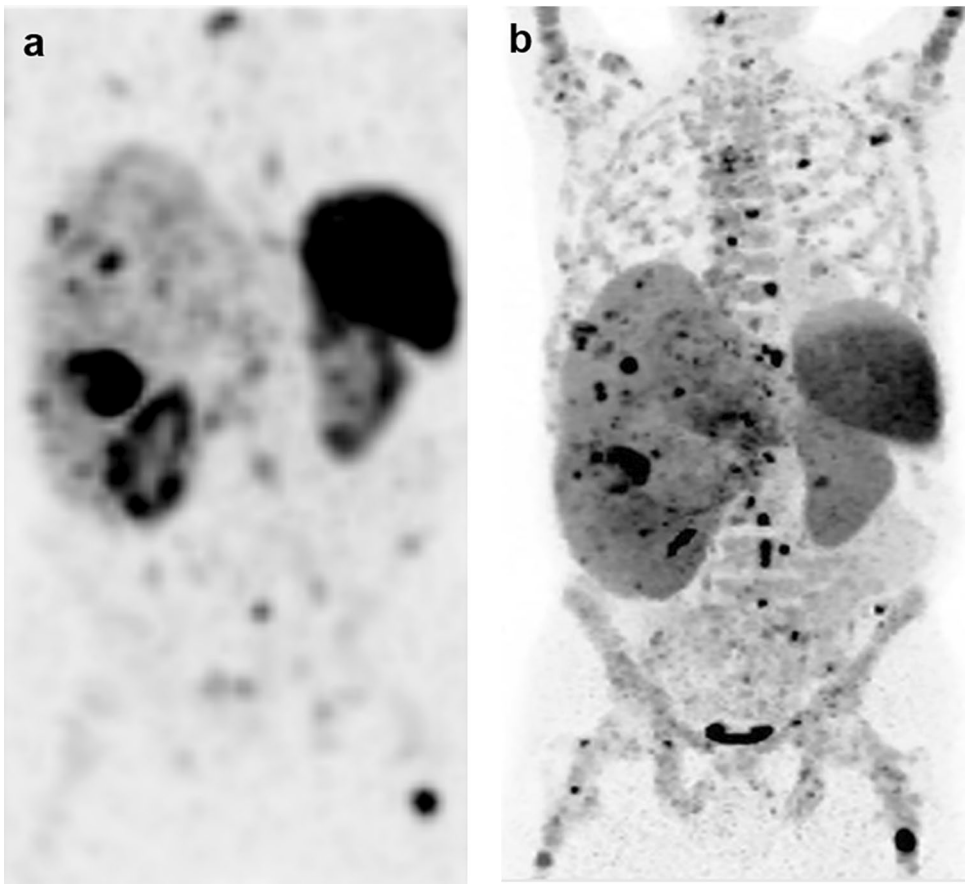

Fig. 1 Incremental value of SSTR PET over somatostatin receptor scintigraphy (SRS). A 66-year-old male with a metastatic well-differentiated NEN. Whole-body planar SRS image (**a**) shows multifocal radiotracer-avid hepatic metastases and a few scattered tracer-avid osseous lesions. Maximum intensity projection (MIP) image (**b**) of the ^{68}Ga-DOTATATE PET/CT shows a substantially higher number of hepatic and osseous lesions with superior resolution

Table 2 Indications for SSTR imaging

1	Baseline staging after histological diagnosis
2	Localization in patients with NEN metastasis of unknown primary
3	Selection of patients for PRRT
4	Staging NENs before surgery
5	Evaluation of a mass suggestive of NEN but not amenable to tissue sampling
6	Monitoring of NENs best seen on SSTR PET
7	Patients with symptoms and biochemical evidence of NEN and inconclusive on CI
8	Restaging for clinical/ biochemical progression with stable disease on CI
9	Restaging after completion of PRRT
10	New indeterminate lesion on CI with unclear progression

SSTR Somatostatin receptor, *NEN* Neuroendocrine neoplasm, *PRRT* Peptide receptor radionuclide therapy, *CI* Conventional imaging

PET/MRI

PET/MRI is a hybrid imaging modality that enables simultaneous acquisition of PET and MRI. It became a reality mainly due to the advent of magnetic field-insensitive solid-state photon detectors of scintillation events. Clinical use of PET/MRI has led to innovative changes in the way both PET and MR data are acquired [22]. PET/MRI has a particularly strong potential for multiparametric evaluation of GEP-NENs. Despite the high accuracy of SSTR PET for imaging of GEP-NENs, evaluation of subtle or small hepatic metastases can be a challenge on SSTR PET/CT due to the high and variable degrees of physiologic hepatic radiotracer uptake (Fig. 2). SSTR PET also does not accurately detect poorly differentiated lesions and tends to have false positives due to physiologic radiotracer uptake in pancreatic uncinate process or intrapancreatic splenules [17]. MRI is the reference standard imaging examination for the evaluation of liver metastases in patients with GEP-NENs. However, characterization of tumor biology and treatment response assessment are known challenges on

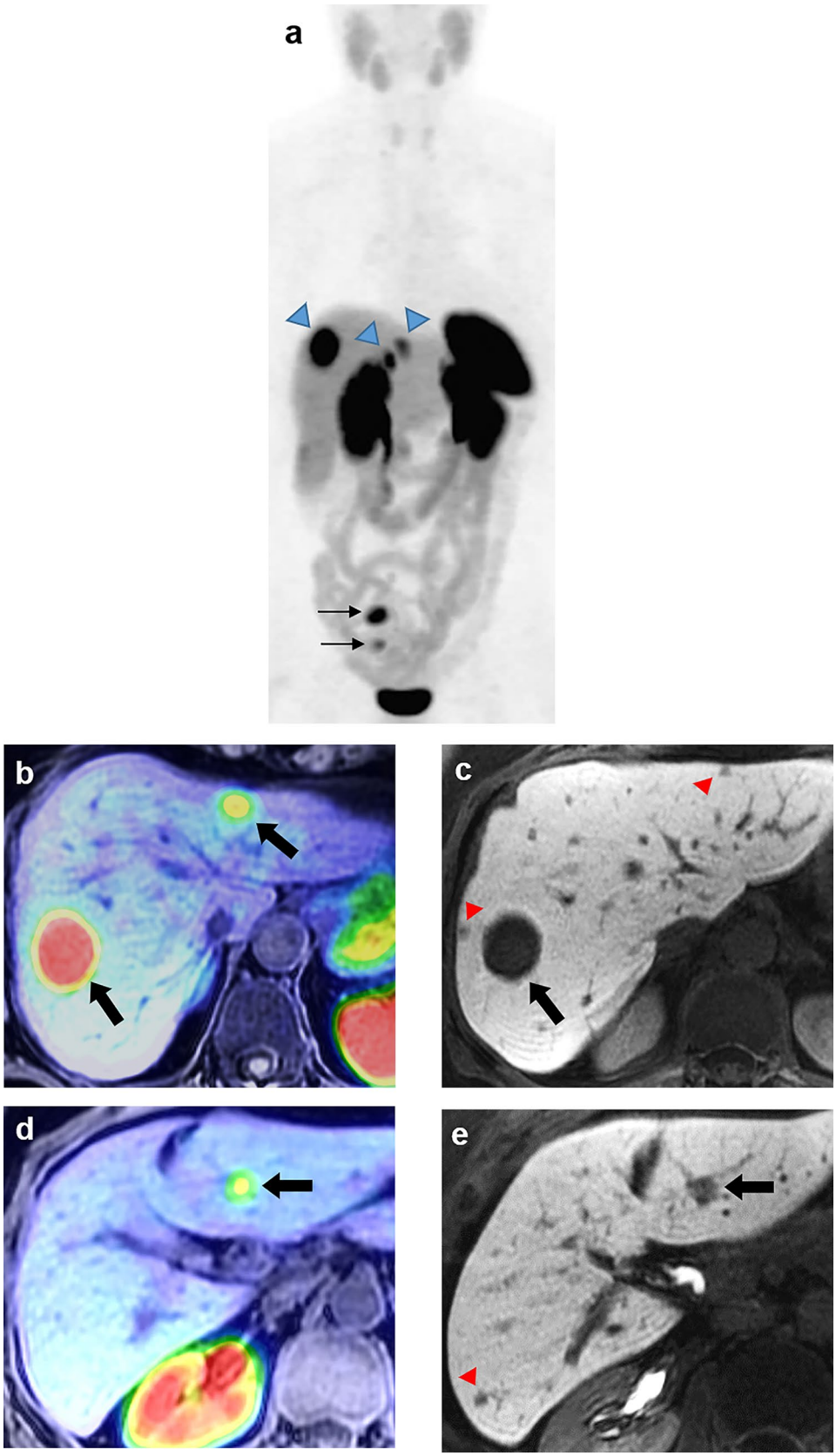

Fig. 2 ^{68}Ga-DOTATATE PET/MRI for evaluation of hepatic metastases. A 76-year-old woman with a G2 ileal NEN. Maximum intensity projection (MIP) image (**a**) of the ^{68}Ga-DOTATATE PET/MRI shows the primary ileal mass with adjacent mesenteric nodal metastases (thin black arrows) and multiple radiotracer-avid liver metastases (blue arrowheads). Axial ^{68}Ga-DOTATATE PET/MRI (**b**, **d**) shows three tracer-avid liver metastases (thick black arrows). The corresponding 20 min delayed hepatobiliary phase images (**c**, **e**) show three additional tiny satellite metastases (red arrowheads) adjacent to the lesions seen on PET (Color figure online)

MRI [23, 24]. Because of these advantages and limitations of individual imaging modalities, many patients with GEP-NENs often undergo both SSTR PET and liver MRI. The combination of PET and MRI into one comprehensive examination offers the prospect of synergistic imaging, streamlined workflow, and a better patient experience.

Appropriate patient selection and optimized imaging workflow are critical requirements for the clinical success of PET/MRI [25]. For instance, patient body habitus is an important consideration. Since the solid-state PET detectors are part of the MR gantry, PET/MRI has a narrower bore (60 cm) compared to most stand-alone MRI scanners (70 cm). At our institution, only patients with body mass index < 40 or anteroposterior abdominal diameter less than 32 cm are scheduled for PET/MRI. To balance patient comfort and scanner throughput, the SSTR PET/MR imaging protocol has been designed to last no more than 60 min. It has two components – the whole-body survey and a focused abdominal PET/MRI. The whole-body component includes multi-bed position PET with co-acquisition of 2-point Dixon three-dimensional (3D) fast-spoiled gradient-recalled echo (FSPGR) imaging at each bed position for anatomic co-localization and attenuation correction. This is immediately followed by focused abdominal PET/MRI, which includes single-bed, list-mode, respiratory-compensated PET acquisition with simultaneous dynamic post-contrast imaging with hepatocyte-specific contrast agent (gadoxetate disodium), T2-weighted imaging, and diffusion-weighted imaging. This protocol offers a synergistic combination of whole-body SSTR PET and optimized multiphase abdominal MRI with dedicated liver PET and has rapidly gained traction in our clinical practice (Fig. 3). Our referring providers use SSTR PET/MRI as an alternative to a combination of SSTR PET/CT and contrast-enhanced CT of the chest, abdomen (biphasic liver protocol), and pelvis. SSTR PET/MRI has the potential to be a sensitive and specific imaging tool for the evaluation of GEP-NENs. Some studies have already shown the promise of PET/MRI for GEP-NENs, but there is a need for validation in larger studies [26–29]. Further, evaluation of lung parenchyma can be suboptimal principally due to limitations of the MR component for detection of sub-centimeter nodules. Recent developments such as free-breathing ultrashort time of echo (UTE)-based PET/MR lung imaging have the potential to address this challenge [30]. Other practical challenges are the high upfront investment that limits the widespread availability of PET/MR, the technical complexity of image acquisition compared with PET/CT, and the complex imaging workflow that often involves multiple radiology subspecialties.

Scoring systems

Krenning score: The Krenning score (Table 3) was initially developed for SRS to assess candidacy for peptide receptor radionuclide therapy (PRRT). However, the Krenning score in its modified form is widely extrapolated to SSTR PET, although there is limited validation for its use with SSTR PET. Besides, the Krenning score from SRS has a limited relationship with the score from SSTR PET [20]. Compared with the Krenning score from SRS, the score on SSTR PET (i.e., modified Krenning score) tends to be higher, especially for lesions less than 2 cm [20, 31]. On the other hand, the score tends to be lower in patients with a very high tumor burden. This is because of the preferential radiotracer sequestration in the NEN lesions, which causes a decrease in the physiologic uptake by the spleen and liver; this is called the 'sink effect' (Fig. 4). These nuances are

Table 3 Krenning score

Grade 1	Uptake similar to the background
Grade 2	Uptake greater than the background but less than or equal to liver
Grade 3	Uptake greater than liver but less than spleen
Grade 4	Uptake greater than spleen

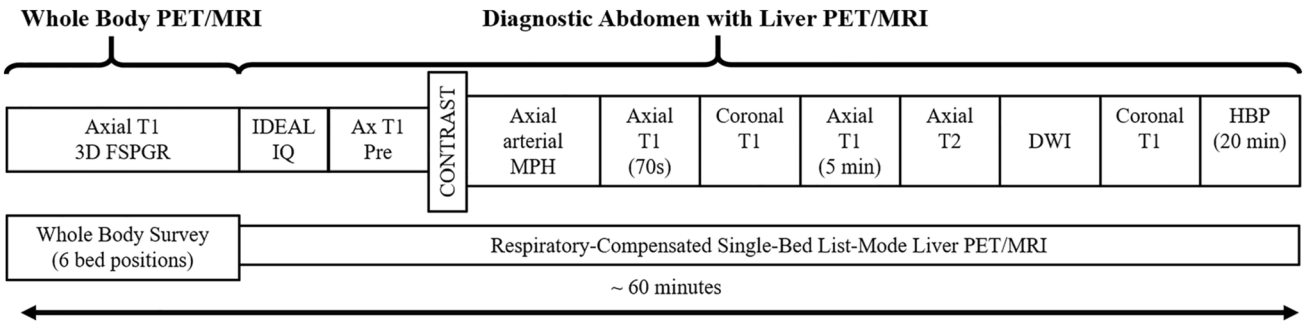

Fig. 3 ^{68}Ga-DOTATATE PET/MRI protocol at our institution. *FSPGR* Fast-spoiled gradient-recalled echo, *IDEAL IQ* Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation, *MPH* Multiphase, *Ax* Axial, *DWI* Diffusion-weighted imaging, *HBP* Hepatobiliary phase. The total protocol duration is around 60 min

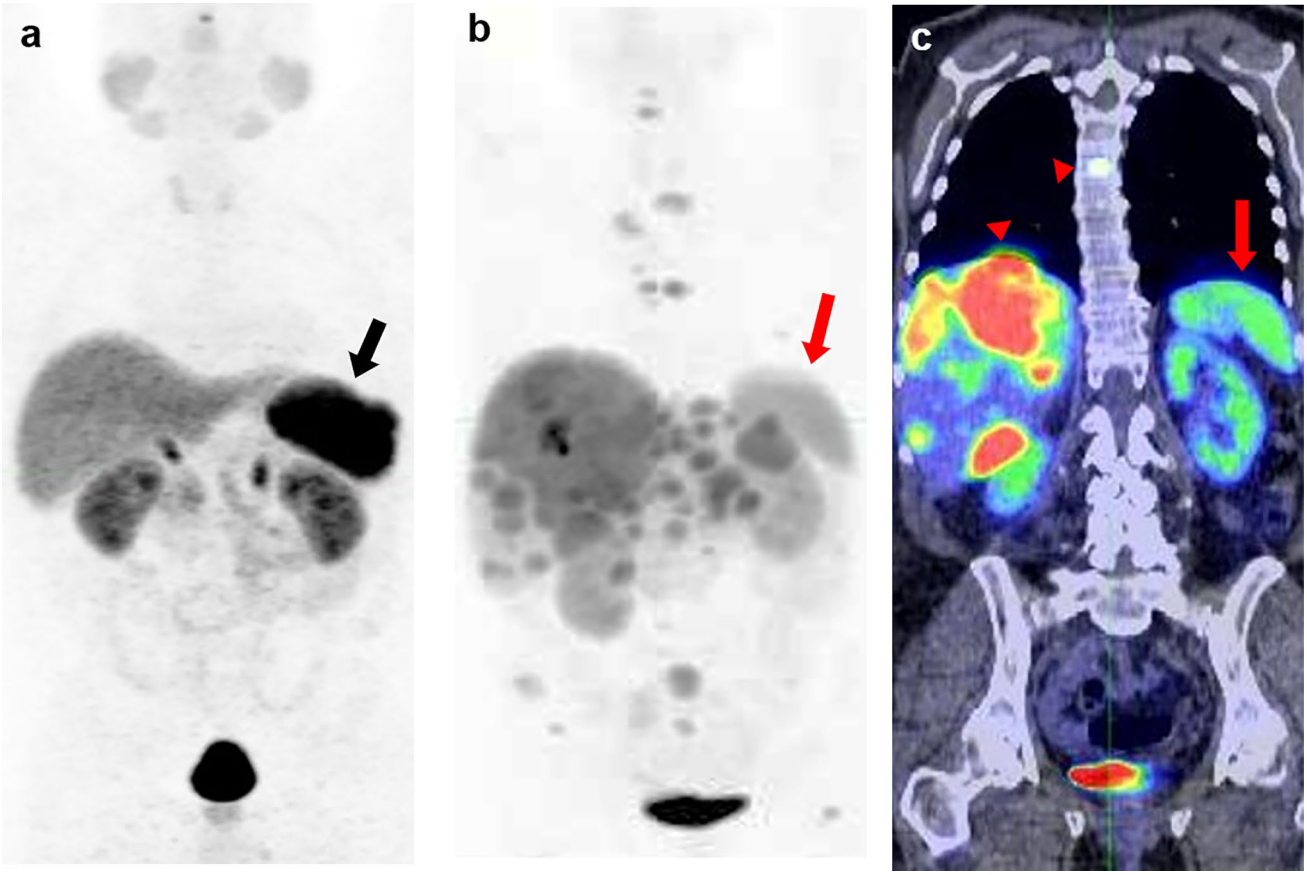

Fig. 4 Normal biodistribution of ^{68}Ga-DOTATATE and the sink effect. Maximum intensity projection (MIP) image of a ^{68}Ga-DOTATATE PET/CT shows the normal biodistribution of ^{68}Ga-DOTATATE (**a**). Note the pronounced physiologic uptake in the spleen (black arrow). MIP (**b**) and coronal ^{68}Ga-DOTATATE PET/CT (**c**) images of a 62-year-old male with metastatic G2 GEP-NEN show sequestration of radiotracer in the extensive metastatic osseous and liver lesions (red arrowhead) with a consequent marked decrease in the physiologic splenic uptake (red arrow), this is called the 'sink effect' (Color figure online)

particularly relevant when the modified Krenning score is used to determine eligibility for PRRT.

SSTR-RADS: SSTR-RADS is a 5-point scale-based scoring system used for the standardized classification and reporting of SSTR PET. It seeks to provide an objective numerical grading based on the level of confidence in the presence of a lesion, the most appropriate next step in management, and potential eligibility for PRRT. Based on the uptake pattern, the lesions are classified into five groups, with recommendations for each group's next step in management (Table 4). SSTR-RADS has been demonstrated to have a high interobserver agreement [32]. SSTR-RADS has several advantages over the Krenning score. The Krenning score only compares the uptake in a lesion to the uptake in the liver or spleen. In contrast, SSTR-RADS entails the assessment of the entire tumor burden while considering information from all available imaging modalities (both molecular and cross-sectional imaging). These advantages have the potential to influence treatment decisions. For instance, the Krenning score does not account for SSTR-negative neoplasms. Therefore, it does not provide information about disease heterogeneity, which can be a challenge in patients with both SSTR-positive and SSTR-negative lesions. These patients may be candidates for combination therapies such as PRRT with either chemotherapy or loco-regional therapy. The use of SSTR-RADS in clinical practice may face resistance from radiologists due to its complexity and the potential to impact their workflow negatively. Prospective multicenter studies are warranted to demonstrate the benefit of SSTR-RADS for response and outcome prediction, which will facilitate its adoption in clinical practice.

SSTR PET in the context of PRRT

PRRT is the therapeutic use of radiolabeled molecules such as somatostatin analogs (SSA) that target the SSTRs on NENs. PRRT represents a precision medicine paradigm that tailors a minimally invasive treatment specific to the biological profile of the tumor. SSTR PET is the new reference standard investigation for patient selection for PRRT,

Table 4 Overview of SSTR-RADS

SSTR-RADS	Finding	Uptake level*	Example	Recommendation	Candidate for PRRT
1 (Benign)	Benign lesions which are biopsy proven or pathognomonic on CI				
1A	No SSTR uptake	1		–	No
1B	Increased focal uptake	2/3	BPH nodule	–	No
2 (Likely benign)	Low level or nonspecific SSTR uptake at site atypical for NEN metastasis	1	Axillary nodes/ degenerative bone lesions	–	No
3 (Indeterminate)	Findings that are suggestive of but not definitive for NEN			Further workup required	
3A	Equivocal uptake in soft tissue sites typical for metastasis	1 – 2	Regional LN	Biopsy or F/u imaging in 3 months	No
3B	Bone uptake that is not atypical for NEN metastasis	1 – 2		F/u imaging in 3 months	Yes (if multiple)
3C	SSTR-expressing non-NEN	3	Breast uptake	Biopsy	No
3D	High suspicion of malignant NEN, but no SSTR uptake	–	High-grade NEN	^{18}F-FDG PET	No
4 (Highly likely)	Intense uptake in a typical location *without* characteristic features on CI	3	Small regional LN	Biopsy not needed	Yes
5 (Almost certain)	Intense uptake in a typical location *with* characteristic features on CI	3	A liver lesion with similar finding on CI	Negative biopsy has a high chance of being false negative	Yes

*Levels of uptake: 1-less than or equal to blood pool, 2-greater than blood pool but less than or equal to the liver, and 3-greater than the liver

SSTR-RADS Somatostatin receptor PET-reporting and data system, *PRRT* Peptide receptor radionuclide therapy, *CI* Conventional imaging, *BPH* Benign prostatic hyperplasia, *NEN* Neuroendocrine neoplasm, *LN* Lymph node, *F/u* follow-up

endorsed by the National Comprehensive Cancer Network guidelines [33]. Only patients with tumors that sufficiently express SSTRs on SSTR PET qualify for treatment; this provides an optimal selection strategy. In contrast, patients with lesions that demonstrate lower SSTR uptake are not eligible for PRRT. Typically, the threshold for positive expression on SSTR PET that would lead to PRRT consideration is defined as tumor uptake more than the liver or a Krenning score > 2 [34, 35]. SUV-based thresholds of positive SSTR expression on SSTR PET have been proposed [36, 37]. However, due to the significant variability and lack of standardization of SUV measurements on SSTR PET, clinical adoption of SUV-based criteria is not feasible. In addition to SSTR expression, SSTR PET also provides personalized information pertinent to management, like the detection of SSTR-negative lesions that may require additional targeted therapy.

Response assessment and outcomes prediction

Morphology or size-based response assessment criteria are suboptimal for NENs due to their low growth rate and since systemic therapies tend to stabilize rather than shrink the tumor. Post-therapy SSTR PET has shown variable results for treatment response evaluation in NENs and is further confounded by other challenges. Standard PET response assessment criteria such as PERCIST and the EORTC criteria cannot be directly translated to SSTR PET due to the significant variability in SUVs on SSTR PET. In addition to scanner-related factors, this variability can also be attributed to the widespread therapeutic usage of long-acting SSAs, which tend to decrease physiologic radiotracer uptake and increase tumoral uptake after long-term use [38]. Besides, the diverse treatment options, each with different tumor involution mechanisms, are not amenable to a single response assessment criterion. Due to these challenges, response assessment in clinical practice is often centered on the disappearance of known lesions to indicate favorable treatment response or the detection of new lesions to indicate disease progression. This paradigm is endorsed by multidisciplinary guidelines [18]. In the future, a combination of molecular imaging and blood-based biomarkers may improve treatment response assessment in patients with

NENs [39]. For instance, the NETest analyzes 51 specific circulating mRNA sequences specific to GEP-NENs and has a high accuracy for response assessment of small intestinal and pancreatic NENs [39–42]. Recently, it has been demonstrated that a persistently positive NETest after a seemingly complete resection predicts early radiologic recurrence with high accuracy [43, 44]. Integration of this information with imaging parameters from SSTR PET could be incremental due to their mechanistic differences.

On the other hand, the prognostic and predictive significance of SSTR expression has been validated. In general, higher uptake on baseline pre-therapy SSTR PET correlates with superior post-PRRT outcomes [36, 37, 45–47]. Furthermore, volumetric PET metrics such as SSTR-expressing tumor volume (SSTR-TV), which represents the total tumor volume with SSTR expression above a threshold (e.g., 50% of the SUV_{max}), and total lesion SSTR expression (TL-SSTR), which is the product of SSTR-TV and SUV_{mean} correlate with post-PRRT outcomes such as progression-free survival and time-to-new treatment [48–51].

Pitfalls of SSTR PET

It is imperative to be aware of potential pitfalls and sites of physiologic uptake on SSTR PET that can bias its interpretation. The maximum physiologic uptake of ^{68}Ga-DOTATATE is in the spleen, followed by the kidneys, adrenals, and liver with variable uptake in the stomach, pituitary gland, head of the pancreas, thyroid gland, and uterus (Fig. 4) [52]. Physiologic intense uncinate process uptake occurs in up to 30% of patients and can mimic a neoplasm [53, 54]. This occurs due to the high physiologic density of SSTR expression in the islet cells of the uncinate process [55]. This physiologic uptake can often be differentiated from a neoplasm by its relatively non-circumscribed nature and characteristic curvilinear shape, which is best appreciated on coronal maximum intensity projection images. Apart from the uncinate process, low-level uptake can also be seen throughout the pancreas due to scattered islet cell clusters.

The liver shows high physiologic uptake of ^{68}Ga-labeled SSTR compounds, which can obscure small liver metastases on SSTR PET. Newer radiotracers like ^{64}Cu-DOTATATE have the advantage of lower physiologic liver uptake. A combined PET/MRI protocol with hepatobiliary contrast agents like gadoxetate also helps improve diagnostic confidence and accuracy (Fig. 2) [17, 22].

Splenunculi near the pancreatic tail can be confused with a NEN (either a primary tumor or a peritoneal deposit). Splenunculi often demonstrate lower SSTR uptake than the spleen, likely due to their lower vascularity, and differentiation solely on SSTR PET is usually not possible. A denatured red blood cell SPECT or ^{99}Tc-labeled sulfur-colloid scan is confirmatory [35]. Splenunculi have high uptake on these scintigraphic studies, whereas NENs tend to be photopenic (Fig. 5). In patients with a very high burden of SSTR-avid metastatic disease, the combination of low background and high radiotracer uptake can lead to a "sink effect", which refers to high radiotracer sequestration in diseased organs with consequent reduction at sites of physiologic uptake (e.g., spleen). This phenomenon impacts PET-scoring systems (e.g., Krenning score) as well as PRRT dose considerations [56].

Osteoblasts also tend to have SSTR expression. Therefore, variable degrees of radiotracer uptake can be seen in osteoblastic lesions like fractures, osteoblastic metastasis, Paget's disease, and fibrous dysplasia. For instance, osseous hemangiomas can be mistaken for metastases as they often show tracer uptake on SSTR PET (Fig. 6). In such instances, their characteristic appearance on the attenuation correction CT component—bone demineralization with thickened trabeculae manifesting as vertical striation on sagittal images ("corduroy sign") and as small punctate areas of sclerosis on axial images ("polka-dot" appearance) can help with correct interpretation [57]. However, differentiation from metastasis can be difficult on PET/MRI because the characteristic morphology of these lesions may not be appreciated on the MR component. In addition, leukocytes and macrophages also express SSTR, which can result in variable radiotracer uptake at sites of infection or inflammation.

Numerous non-neuroendocrine neoplasms such as meningiomas and epithelial tumors (e.g., lung, esophageal, breast, colorectal, and testicular) can show variable uptake on SSTR PET. In addition, benign lesions such as thyroid adenomas, hyperplastic prostate nodules, lymphoid hyperplasia, and serous cystadenomas of the pancreas may also show low-level uptake [53, 58].

^{18}F-FDG PET

^{18}F-FDG PET is complementary to SSTR PET for poorly differentiated or high-grade NENs. Well-differentiated and low-grade NENs tend to have low rates of glucose metabolism. Nevertheless, FDG uptake can be seen in up to 40% of such neoplasms [59]. As the NENs de-differentiate towards high-grade NENs and NECs, there is upregulation of glucose transporters and downregulation of SSTRs, referred to as the 'flip-flop' phenomenon. There also tends to be significant intra-lesional and inter-lesional variability in any given patient (Fig. 7). Therefore, some clinical practices perform both SSTR and FDG PET in many patients to characterize disease heterogeneity, risk stratify disease groups, and assess the potential of response to PRRT. For instance, the combination of high SSTR and low FDG uptake portends a high likelihood of response to PRRT. Secondly, FDG PET can guide treatment options to augment PRRT, such as targeted

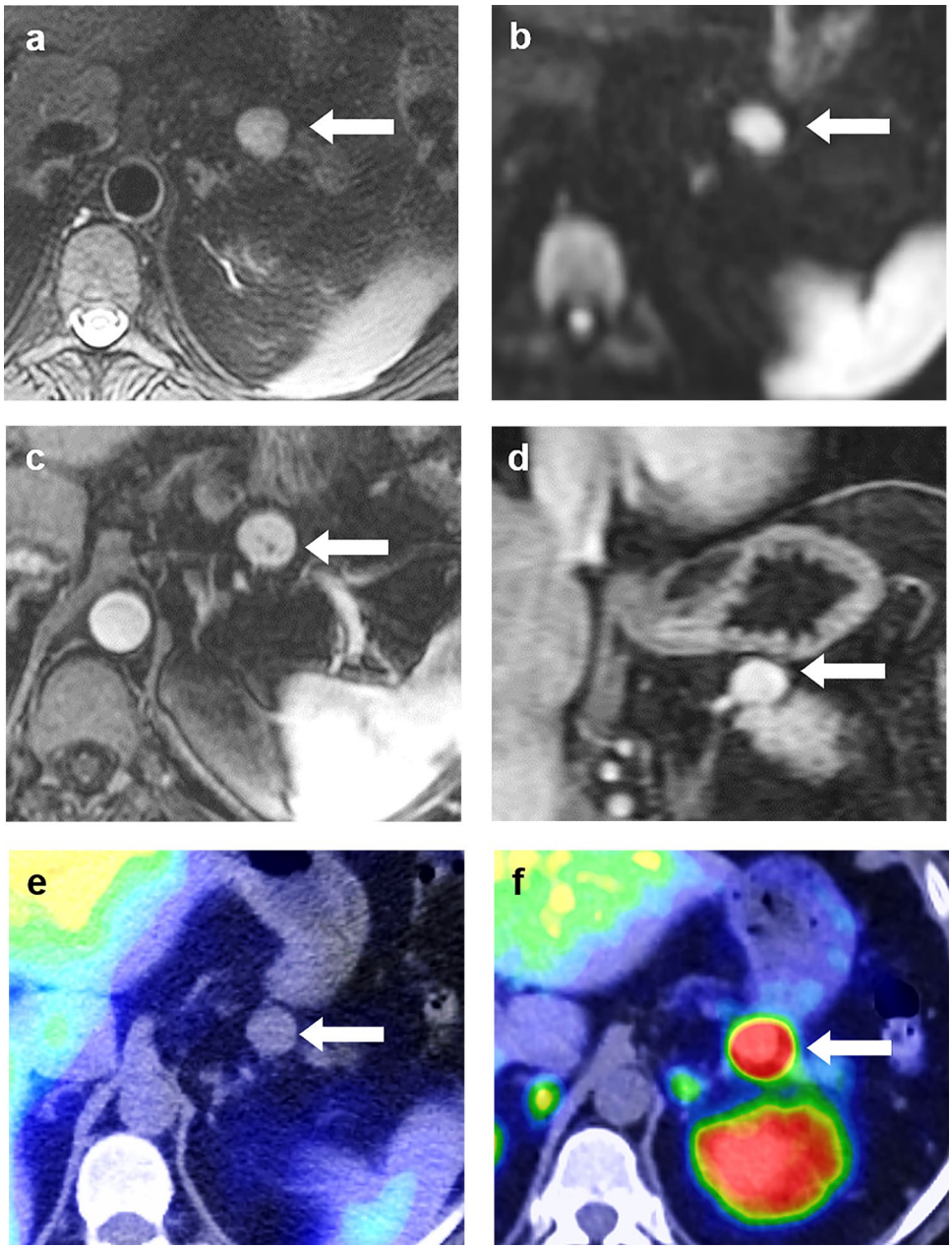

Fig. 5 SSTR PET and sulfur-colloid SPECT for differentiation of splenunculus from NEN. MR images (**a**–**d**) of a 50-year-old woman showed a well-circumscribed mass near the pancreatic tail with signal intensity and post-contrast enhancement mirroring that of the spleen on T2-weighted image (**a**), diffusion-weighted image (**b**), arterial phase image (**c**), and coronal delayed post-contrast image (**d**). A ^{99m}Tc sulfur-colloid SPECT (**e**) demonstrated no radiotracer uptake in the mass, which excluded the possibility of a splenunculus and suggested NEN as the etiology. Subsequent ^{68}Ga-DOTATATE PET/CT demonstrated intense radiotracer uptake in the mass and the diagnosis of well-differentiated NEN was confirmed on histopathology evaluation of the distal pancreatectomy specimen

external radiation to FDG-avid but SSTR-negative lesions. Therefore, a combination of FDG and SSTR PET can facilitate personalized treatment decisions for NENs.

FDG PET also has strong prognostic utility in NENs [60–62]. Lesions with high FDG and low SSTR uptake have a worse prognosis than those with high SSTR and low FDG uptake. In NECs, a maximum standardized uptake value (SUV_{max}) > 3 on FDG PET is an independent risk factor for disease progression [59, 63]. FDG PET may also provide prognostic information incremental to the WHO grade. In patients with G3 NENs, uptake on FDG PET correlates strongly with overall survival (OS) [61]. This can potentially help stratify G3 NENs into low and high-risk groups, which is currently not possible on histology. Similarly, FDG may also stratify low-grade NENs into low and high-risk groups [64]. Based on these data, some groups recommend FDG PET in the routine workup of NENs [61].

The NETPET score is a recently described imaging metric that seeks to incorporate information from both FDG and SSTR PET into a single index (Table 5) [65]. The lesion that shows maximum FDG uptake relative to its SSTR uptake is used as the index lesion for categorization since this lesion likely has the most aggressive phenotype. The NETPET score correlates with the WHO grade and the OS (independent of histological grade) [66]. Another metric, the FDZ score, can identify a subset of patients with

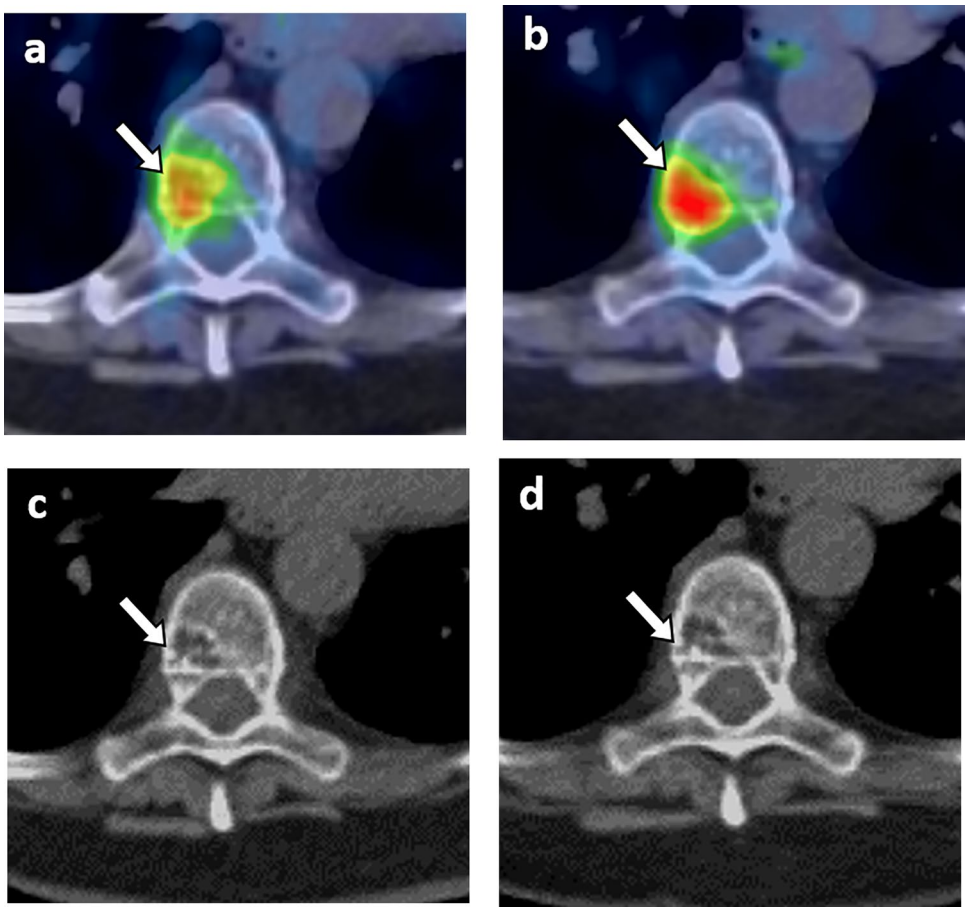

Fig. 6 Vertebral hemangioma mimicking metastasis on ^{68}Ga-DOTATATE PET/CT. ^{68}Ga-DOTATATE PET/CT images in a 61-year-old woman with Multiple Endocrine Neoplasia type 2A. Focal radiotracer uptake is seen in a thoracic vertebral body (**a**) (white arrow), which was suggestive of being a metastasis. However, the attenuation correction CT (**c**) shows punctate sclerosis ("polka dot sign") in a pattern that is characteristic of a vertebral hemangioma. ^{68}Ga-DOTATATE PET/CT obtained 6 months later (**b**, **d**) shows an increase in radiotracer uptake (**b**) but with a stable CT appearance (**d**). The stability and the characteristic morphology on CT confirmed the etiology as osseous hemangioma. The lesion remained stable on an MRI performed 1 year later (not shown)

G3 GEP-NENs with better outcomes [67]. The FDZ score normalizes the different reference SUV_{max} values from the dual-tracer PET to obtain a 'Z score' for each tracer (FDZ score = $Z_{FDG} - Z_{DOTATATE}$). The FDZ score strongly correlates with OS in patients with G3 NENs, but prospective validation is needed. The clinical utility of these metrics remains uncertain because SSTR and FDG PET are not routinely performed together, and co-registration of data from both scans is needed for accurate calculation.

Other radiotracers

^{18}F-Fluorodihydroxyphenylalanine (^{18}F-FDOPA), a radiotagged precursor for serotonin biosynthesis, is preferentially taken up by NENs, particularly those arising from the midgut [68, 69]. Small head-to-head comparison studies in patients with small intestinal NENs have shown higher sensitivity and superior lesion detection rates compared with ^{68}Ga-labeled-SSAs [70–72]. Therefore, ^{18}F-FDOPA can be a potential problem-solving tool in patients with a high index of suspicion for a midgut NEN and negative SSTR imaging [73].

Radiolabeled glucagon-like peptide-1 receptor (GLP-1R) analogs (e.g., ^{68}Ga-DOTA-exendin-4) are currently the most sensitive radiotracers for benign insulinoma localization. Insulinomas are the most common functioning NEN. Unfortunately, identification is often difficult on SSTR PET and cross-sectional imaging due to their poor SSTR expression and small size [74–77]. The European Neuroendocrine Tumor Society (ENTS) guidelines endorse the use of GLP-1R PET for patients with life-threatening hypoglycemia in whom cross-sectional imaging and endoscopic ultrasound cannot localize the neoplasm [78]. Malignant insulinomas, on the other hand, express GLP-1R in less than 40% of cases; fortunately, these neoplasms have high SSTR expression, which renders them amenable for detection on SSTR PET.

SSTR antagonists (e.g., ^{68}Ga-NODAGA-JR11) are novel radiotracers that, unlike agonists, neither activate the SSTR nor are internalized, yet retain a high affinity for SSTRs due to the higher number of potential binding sites [17]. Advantages include their rapid tumor binding, high tumor-to-background ratio, rapid blood clearance, and optimal biodistribution profiles in patients with metastatic NENs [79]. Despite early evidence that suggests ^{68}Ga-NODAGA-JR11 demonstrates a higher lesion-based detection sensitivity than ^{68}Ga-DOTATOC, further comparative studies are needed to

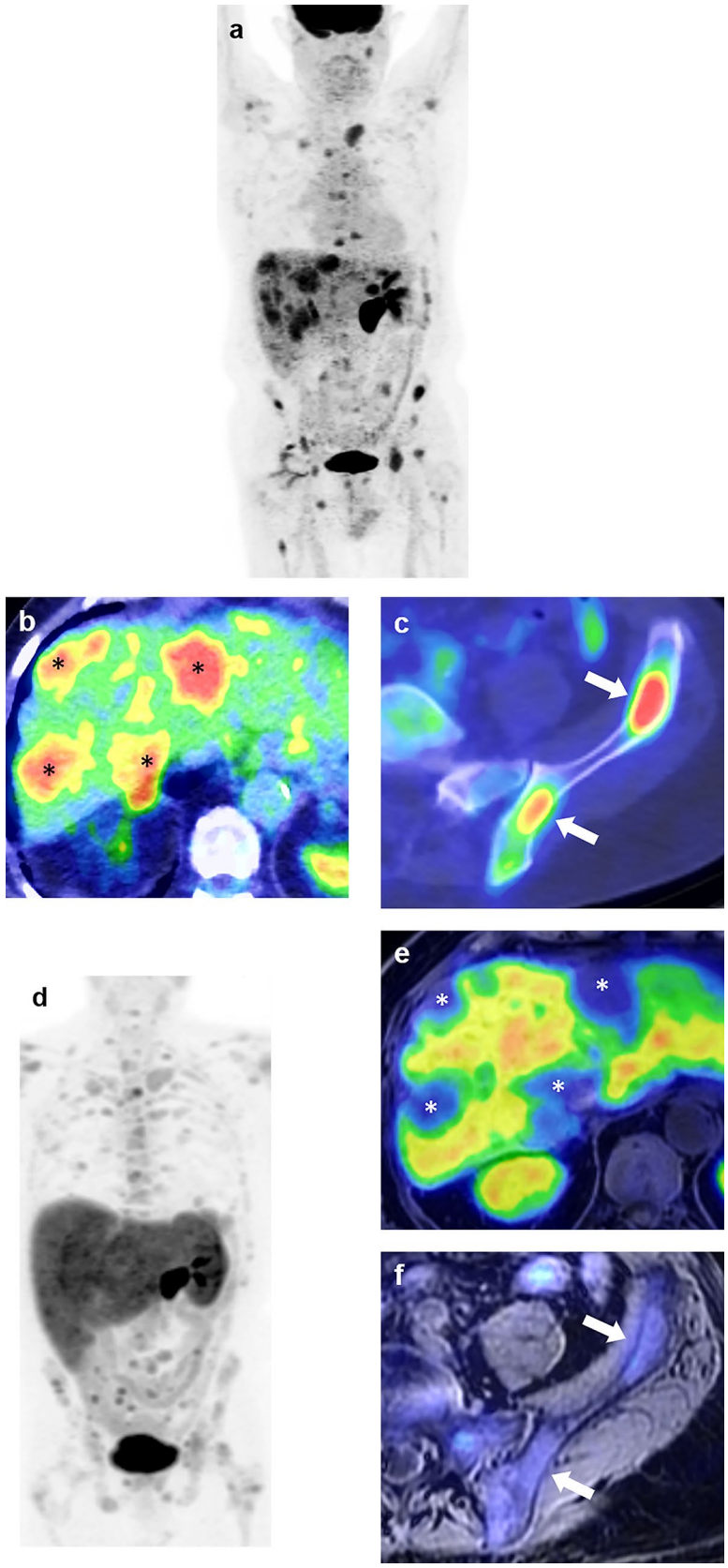

Fig. 7 Dual-tracer PET imaging with ^{18}F-FDG and ^{68}Ga-DOTATATE. A 79-year-old gentleman with a metastatic large cell NEC of GI origin. FDG PET/CT (**a**–**c**) shows multiple radiotracer-avid liver (asterisks) and osseous metastases (arrows). Subsequent ^{68}Ga-DOTATATE PET/MRI (**d**–**f**) showed the absence of radiotracer uptake in both the liver (asterisks) and the osseous metastases (arrows) (**e**, **f**) consistent with the expected receptor distribution of NECs. The NETPET score for this patient would be P5 since the target lesions (3 in the liver) were photopenic on SSTR PET but radiotracer avid on FDG PET. Note the high spatial co-registration of the PET and the MR data on the fused PET/MR image (**e**, **f**) due to simultaneous co-acquisition of the two datasets

Table 5 NETPET scoring system for dual-tracer SSTR/FDG PET

	P0	P1	P2*	P3*	P4*	P5
SSTR	Negative	Positive	SSTR > FDG	SSTR = FDG	SSTR < FDG	Negative
FDG	Negative	Negative				Positive

*Grade P2 to P4 are further subclassified based on the number of lesions into a = 1–2 lesions and b = ≥ 3 lesions

SSTR Somatostatin receptor, *FDG* fluorodeoxyglucose

assess the differences in the diagnostic performance of SSTR antagonists versus agonists [80].

^{18}F-AlF-NOTA-octreotide (^{18}F-OC) is a novel ^{18}F-labeled-SSA with favorable kinetic and imaging characteristics compared to ^{68}Ga-labeled-SSAs [81, 82]. ^{18}F-OC has good tumor uptake and a higher liver tumor-to-background ratio than ^{68}Ga-labeled SSAs, which is reflected by the higher hepatic lesion detection rate [81, 83]. If validated for imaging of NENs, ^{18}F-OC has the potential to be an alternative to ^{68}Ga-DOTATATE in centers where ^{68}Ge/^{68}Ga generators are not available.

Conclusion

Advances in the molecular imaging of GEP-NENs have led to improved diagnosis, staging, understanding of their biology, and personalized patient management. SSTR PET is the new reference standard imaging examination for GEP-NENs and is particularly critical in the context of PRRT eligibility. SSTR PET/MRI with liver-specific contrast agent offers the prospect of one-stop-shop imaging for the evaluation of GEP-NENs. It is crucial to be aware of the potential pitfalls and areas of physiologic uptake on SSTR PET to avoid inadvertent interpretation errors. FDG PET is complementary to SSTR PET, especially in the context of high-grade NENs and NECs. Novel radiotracers under investigation have the potential to overcome existing limitations in the molecular imaging of GEP-NENs. Knowledge gaps in quantitative evaluation of molecular imaging studies and their role in response assessment are active research areas.

Acknowledgements None.

Funding Dr. Rajamohan, Dr. Khasawneh, Dr. Singh, Dr. Suman, Dr. Majumder, and Dr. Goenka have no funding to disclose for the current work. Unrelated to this work (Dr. Goenka): Research grant from the Champions for Hope Pancreatic Cancer Research Program of the Funk-Zitiello Foundation; Advance the Practice Award from the Department of Radiology, Mayo Clinic, Rochester, Minnesota; CA190188, Department of Defense (DoD), Office of the Congressionally Directed Medical Research Programs (CDMRP); R01CA256969, National Cancer Institute (NCI) of the National Institutes of Health (NIH); Institutional research grant from Sofie Biosciences; Advisory Board (ad hoc), BlueStar Genomics.

Declarations

Conflict of interest Dr. Rajamohan, Dr. Khasawneh, Dr. Singh, Dr. Suman, Dr. Majumder, Dr. Halfdanarson, and Dr. Goenka have no conflicts of interest.

References

1. Fraenkel, M., M.K. Kim, A. Faggiano, et al.(2012) "Epidemiology of gastroenteropancreatic neuroendocrine tumours." Review of Best Pract Res Clin Gastroenterol. 26, no. (6): 691-703. https://doi.org/https://doi.org/10.1016/j.bpg.2013.01.006.
2. Korse, C.M., B.G. Taal, M.L. van Velthuysen, et al.(2013) "Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry." Review of Eur J Cancer. 49, no. (8): 1975-83. https://doi.org/https://doi.org/10.1016/j.ejca.2012.12.022.
3. Xu, Z., L. Wang, S. Dai, et al.(2021) "Epidemiologic Trends of and Factors Associated With Overall Survival for Patients With Gastroenteropancreatic Neuroendocrine Tumors in the United States." Review of JAMA Netw Open. 4, no. (9): e2124750. https://doi.org/https://doi.org/10.1001/jamanetworkopen.2021.24750.
4. Lee, M.R., C. Harris, K.J. Baeg, et al.(2018) "Incidence trends of gastroenteropancreatic neuroendocrine tumors in the United States from 1975 to 2012." Review of Journal of Clinical Oncology. 36, no. (4_suppl): 231-231. https://doi.org/https://doi.org/10.1200/JCO.2018.36.4_suppl.231.
5. Boyar Cetinkaya, R., B. Aagnes, E. Thiis-Evensen, et al.(2017) "Trends in Incidence of Neuroendocrine Neoplasms in Norway: A Report of 16,075 Cases from 1993 through 2010." Review of Neuroendocrinology. 104, no. (1): 1-10. https://doi.org/https://doi.org/10.1159/000442207.
6. Kaçmaz, E., A.F. Sarasqueta, S. van Eeden, et al.(2021) "Update on Incidence, Prevalence, Treatment and Survival of Patients with Small Bowel Neuroendocrine Neoplasms in the Netherlands." Review of World J Surg. 45, no. (8): 2482-2491. https://doi.org/https://doi.org/10.1007/s00268-021-06119-y.
7. Hallet, J., C.H. Law, M. Cukier, et al.(2015) "Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes." Review of Cancer. 121, no. (4): 589-97. https://doi.org/https://doi.org/10.1002/cncr.29099.
8. Oladejo, A.O.(2009) "GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (GEP-NETs) - APPROACH TO DIAGNOSIS AND MANAGEMENT." Review of Ann Ib Postgrad Med. 7, no. (2): 29-33. https://doi.org/https://doi.org/10.4314/aipm.v7i2.64085.
9. Crona, J. and B. Skogseid.(2016) "GEP- NETS UPDATE: Genetics of neuroendocrine tumors." Review of Eur J Endocrinol. 174, no. (6): R275-90. https://doi.org/https://doi.org/10.1530/eje-15-0972.

10. Lesén, E., D. Granfeldt, A. Berthon, et al.(2019) "Treatment Patterns and Survival among Patients with Metastatic Gastroenteropancreatic Neuroendocrine Tumours in Sweden - a Population-based Register-linkage and Medical Chart Review Study." Review of J Cancer. 10, no. (27): 6876-6887. https://doi.org/https://doi.org/10.7150/jca.32381.
11. American Cancer Society. *Survival rates for pancreatic neuroendocrine tumor*. 2021, January 26; Available from: https://www.cancer.org/cancer/pancreatic-neuroendocrine-tumor/detection-diagnosis-staging/survival-rates.html.
12. Nagtegaal, I.D., R.D. Odze, D. Klimstra, et al.(2020) "The 2019 WHO classification of tumours of the digestive system." Review of Histopathology. 76, no. (2): 182-188. https://doi.org/https://doi.org/10.1111/his.13975.
13. Bałdys-Waligórska, A. and A. Nowak.(2021) "Neuroendocrine neoplasms of the digestive system – current classification and terminology." Review of Nowotwory. Journal of Oncology. 71, no. (1): 26-37. https://doi.org/https://doi.org/10.5603/njo.2021.0005.
14. Remes, S.M., H.L. Leijon, T.J. Vesterinen, et al.(2019) "Immunohistochemical Expression of Somatostatin Receptor Subtypes in a Panel of Neuroendocrine Neoplasias." Review of J Histochem Cytochem. 67, no. (10): 735-743. https://doi.org/https://doi.org/10.1369/0022155419856900.
15. Gabriel, M., C. Decristoforo, D. Kendler, et al.(2007) "68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT." Review of J Nucl Med. 48, no. (4): 508-18. https://doi.org/https://doi.org/10.2967/jnumed.106.035667.
16. Pfeifer, A., U. Knigge, T. Binderup, et al.(2015) "64Cu-DOTATATE PET for Neuroendocrine Tumors: A Prospective Head-to-Head Comparison with 111In-DTPA-Octreotide in 112 Patients." Review of J Nucl Med. 56, no. (6): 847-54. https://doi.org/https://doi.org/10.2967/jnumed.115.156539.
17. Panda, A., I. Garg, G.B. Johnson, et al.(2019) "Molecular radionuclide imaging of pancreatic neoplasms." Review of Lancet Gastroenterol Hepatol. 4, no. (7): 559-570. https://doi.org/https://doi.org/10.1016/s2468-1253(19)30081-0.
18. Hope, T.A., E.K. Bergsland, M.F. Bozkurt, et al.(2018) "Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors." Review of Journal of Nuclear Medicine. 59, no. (1): 66-74. https://doi.org/https://doi.org/10.2967/jnumed.117.202275.
19. Johnbeck, C.B., U. Knigge, A. Loft, et al.(2017) "Head-to-Head Comparison of (64)Cu-DOTATATE and (68)Ga-DOTATOC PET/CT: A Prospective Study of 59 Patients with Neuroendocrine Tumors." Review of J Nucl Med. 58, no. (3): 451-457. https://doi.org/https://doi.org/10.2967/jnumed.116.180430.
20. Park, S., A.S. Parihar, L. Bodei, et al.(2021) "Somatostatin Receptor Imaging and Theranostics: Current Practice and Future Prospects." Review of J Nucl Med. 62, no. (10): 1323-1329. https://doi.org/https://doi.org/10.2967/jnumed.120.251512.
21. Hicks, R.J., P. Jackson, G. Kong, et al.(2019) "(64)Cu-SARTATE PET Imaging of Patients with Neuroendocrine Tumors Demonstrates High Tumor Uptake and Retention, Potentially Allowing Prospective Dosimetry for Peptide Receptor Radionuclide Therapy." Review of J Nucl Med. 60, no. (6): 777-785. https://doi.org/https://doi.org/10.2967/jnumed.118.217745.
22. Broski, S.M., A.H. Goenka, B.J. Kemp, et al.(2018) "Clinical PET/MRI: 2018 Update." Review of AJR Am J Roentgenol. 211, no. (2): 295-313. https://doi.org/https://doi.org/10.2214/ajr.18.20001.
23. Garcia-Carbonero, R., R. Garcia-Figueiras, A. Carmona-Bayonas, et al.(2015) "Imaging approaches to assess the therapeutic response of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): current perspectives and future trends of an exciting field in development." Review of Cancer Metastasis Rev. 34, no. (4): 823-42. https://doi.org/https://doi.org/10.1007/s10555-015-9598-5.
24. Neperud, J., A. Mahvash, N. Garg, et al.(2013) "Can imaging patterns of neuroendocrine hepatic metastases predict response yttruim-90 radioembolotherapy?" Review of World J Radiol. 5, no. (6): 241-7. https://doi.org/https://doi.org/10.4329/wjr.v5.i6.241.
25. Panda, A., A.H. Goenka, T.A. Hope, et al.(2020) "PET/Magnetic Resonance Imaging Applications in Abdomen and Pelvis." Review of Magn Reson Imaging Clin N Am. 28, no. (3): 369-380. https://doi.org/https://doi.org/10.1016/j.mric.2020.03.010.
26. Mayerhoefer, M.E., H. Prosch, L. Beer, et al.(2020) "PET/MRI versus PET/CT in oncology: a prospective single-center study of 330 examinations focusing on implications for patient management and cost considerations." Review of Eur J Nucl Med Mol Imaging. 47, no. (1): 51-60. https://doi.org/https://doi.org/10.1007/s00259-019-04452-y.
27. Hope, T.A., M.H. Pampaloni, E. Nakakura, et al.(2015) "Simultaneous (68)Ga-DOTA-TOC PET/MRI with gadoxetate disodium in patients with neuroendocrine tumor." Review of Abdom Imaging. 40, no. (6): 1432-40. https://doi.org/https://doi.org/10.1007/s00261-015-0409-9.
28. Adams, L.C., K.K. Bressem, J. Brangsch, et al.(2020) "Quantitative 3D Assessment of (68)Ga-DOTATOC PET/MRI with Diffusion-Weighted Imaging to Assess Imaging Markers for Gastroenteropancreatic Neuroendocrine Tumors: Preliminary Results." Review of J Nucl Med. 61, no. (7): 1021-1027. https://doi.org/https://doi.org/10.2967/jnumed.119.234062.
29. Berzaczy, D., C. Giraudo, A.R. Haug, et al.(2017) "Whole-Body 68Ga-DOTANOC PET/MRI Versus 68Ga-DOTANOC PET/CT in Patients With Neuroendocrine Tumors: A Prospective Study in 28 Patients." Review of Clin Nucl Med. 42, no. (9): 669-674. https://doi.org/https://doi.org/10.1097/rlu.0000000000001753.
30. Burris, N.S., K.M. Johnson, P.E.Z. Larson, et al.(2016) "Detection of Small Pulmonary Nodules with Ultrashort Echo Time Sequences in Oncology Patients by Using a PET/MR System." Review of Radiology. 278, no. (1): 239-246. https://doi.org/https://doi.org/10.1148/radiol.2015150489.
31. Hope, T.A., J. Calais, L. Zhang, et al.(2019) "(111)In-Pentetreotide Scintigraphy Versus (68)Ga-DOTATATE PET: Impact on Krenning Scores and Effect of Tumor Burden." Review of J Nucl Med. 60, no. (9): 1266-1269. https://doi.org/https://doi.org/10.2967/jnumed.118.223016.
32. Werner, R.A., T. Derlin, S.P. Rowe, et al.(2021) "High Interobserver Agreement for the Standardized Reporting System SSTR-RADS 1.0 on Somatostatin Receptor PET/CT." Review of J Nucl Med. 62, no. (4): 514-520. https://doi.org/https://doi.org/10.2967/jnumed.120.245464.
33. Shah, M.H., W.S. Goldner, A.B. Benson, et al.(2021) "Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology." Review of J Natl Compr Canc Netw. 19, no. (7): 839-868. https://doi.org/https://doi.org/10.6004/jnccn.2021.0032.
34. Hope, T.A., L. Bodei, J.A. Chan, et al.(2020) "NANETS/SNMMI Consensus Statement on Patient Selection and Appropriate Use of (177)Lu-DOTATATE Peptide Receptor Radionuclide Therapy." Review of J Nucl Med. 61, no. (2): 222-227. https://doi.org/https://doi.org/10.2967/jnumed.119.240911.
35. Subramaniam, R.M., M.L. Bradshaw, K. Lewis, et al.(2018) "ACR Practice Parameter for the Performance of Gallium-68 DOTATATE PET/CT for Neuroendocrine Tumors." Review of Clin Nucl Med. 43, no. (12): 899-908. https://doi.org/https://doi.org/10.1097/rlu.0000000000002309.
36. Kratochwil, C., M. Stefanova, E. Mavriopoulou, et al.(2015) "SUV of [68Ga]DOTATOC-PET/CT Predicts Response Probability of PRRT in Neuroendocrine Tumors." Review of Mol Imaging

Biol. 17, no. (3): 313-8. https://doi.org/https://doi.org/10.1007/s11307-014-0795-3.
37. Öksüz, M., L. Winter, C. Pfannenberg, et al.(2014) "Peptide receptor radionuclide therapy of neuroendocrine tumors with (90)Y-DOTATOC: is treatment response predictable by pre-therapeutic uptake of (68)Ga-DOTATOC?" Review of Diagn Interv Imaging. 95, no. (3): 289-300. https://doi.org/https://doi.org/10.1016/j.diii.2013.07.006.
38. Cherk, M.H., G. Kong, R.J. Hicks, et al.(2018) "Changes in biodistribution on (68)Ga-DOTA-Octreotate PET/CT after long acting somatostatin analogue therapy in neuroendocrine tumour patients may result in pseudoprogression." Review of Cancer Imaging. 18, no. (1): 3. https://doi.org/https://doi.org/10.1186/s40644-018-0136-x.
39. Roll, W., M. Weckesser, R. Seifert, et al.(2021) "Imaging and liquid biopsy in the prediction and evaluation of response to PRRT in neuroendocrine tumors: implications for patient management." Review of Eur J Nucl Med Mol Imaging. 48, no. (12): 4016-4027. https://doi.org/https://doi.org/10.1007/s00259-021-05359-3.
40. Malczewska, A., B. Kos-Kudła, M. Kidd, et al.(2020) "The clinical applications of a multigene liquid biopsy (NETest) in neuroendocrine tumors." Review of Adv Med Sci. 65, no. (1): 18-29. https://doi.org/https://doi.org/10.1016/j.advms.2019.10.002.
41. Modlin, I.M., M. Kidd, L. Bodei, et al.(2015) "The clinical utility of a novel blood-based multi-transcriptome assay for the diagnosis of neuroendocrine tumors of the gastrointestinal tract." Review of Am J Gastroenterol. 110, no. (8): 1223-32. https://doi.org/https://doi.org/10.1038/ajg.2015.160.
42. Öberg, K., A. Califano, J.R. Strosberg, et al.(2020) "A meta-analysis of the accuracy of a neuroendocrine tumor mRNA genomic biomarker (NETest) in blood." Review of Ann Oncol. 31, no. (2): 202-212. https://doi.org/https://doi.org/10.1016/j.annonc.2019.11.003.
43. Modlin, I.M., M. Kidd, A. Frilling, et al.(2021) "Molecular Genomic Assessment Using a Blood-based mRNA Signature (NETest) is Cost-effective and Predicts Neuroendocrine Tumor Recurrence With 94% Accuracy." Review of Ann Surg. 274, no. (3): 481-490. https://doi.org/https://doi.org/10.1097/sla.0000000000005026.
44. Modlin, I.M., M. Kidd, K. Oberg, et al.(2021) "Early Identification of Residual Disease After Neuroendocrine Tumor Resection Using a Liquid Biopsy Multigenomic mRNA Signature (NETest)." Review of Ann Surg Oncol. 28, no. (12): 7506-7517. https://doi.org/https://doi.org/10.1245/s10434-021-10021-1.
45. Ambrosini, V., D. Campana, G. Polverari, et al.(2015) "Prognostic Value of 68Ga-DOTANOC PET/CT SUVmax in Patients with Neuroendocrine Tumors of the Pancreas." Review of J Nucl Med. 56, no. (12): 1843-8. https://doi.org/https://doi.org/10.2967/jnumed.115.162719.
46. Ortega, C., R.K.S. Wong, J. Schaefferkoetter, et al.(2021) "Quantitative (68)Ga-DOTATATE PET/CT Parameters for the Prediction of Therapy Response in Patients with Progressive Metastatic Neuroendocrine Tumors Treated with (177)Lu-DOTATATE." Review of J Nucl Med. 62, no. (10): 1406-1414. https://doi.org/https://doi.org/10.2967/jnumed.120.256727.
47. Sharma, R., W.M. Wang, S. Yusuf, et al.(2019) "(68)Ga-DOTATATE PET/CT parameters predict response to peptide receptor radionuclide therapy in neuroendocrine tumours." Review of Radiother Oncol. 141, no.: 108-115. https://doi.org/https://doi.org/10.1016/j.radonc.2019.09.003.
48. Carlsen, E.A., C.B. Johnbeck, T. Binderup, et al.(2020) "(64)Cu-DOTATATE PET/CT and Prediction of Overall and Progression-Free Survival in Patients with Neuroendocrine Neoplasms." Review of J Nucl Med. 61, no. (10): 1491-1497. https://doi.org/https://doi.org/10.2967/jnumed.119.240143.
49. Thuillier, P., V. Liberini, S. Grimaldi, et al.(2021) "Prognostic value of whole-body PET volumetric parameters extracted from (68)Ga-DOTATOC-PET/CT in well-differentiated neuroendocrine tumors." Review of J Nucl Med. no. https://doi.org/https://doi.org/10.2967/jnumed.121.262652.
50. Reddy, R.P., C.R. Schmidtlein, R.G. Giancipoli, et al.(2021) "The quest for an accurate functional tumor volume with (68)Ga-DOTATATE PET/CT." Review of J Nucl Med. no. https://doi.org/https://doi.org/10.2967/jnumed.121.262782.
51. Ebbers, S.C., M. Heimgartner, M.W. Barentsz, et al.(2021) "Gallium-68-somatostatin receptor PET/CT parameters as potential prognosticators for clinical time to progression after peptide receptor radionuclide therapy: a cohort study." Review of Eur J Hybrid Imaging. 5, no. (1): 22. https://doi.org/https://doi.org/10.1186/s41824-021-00116-z.
52. Özgüven, S., N. Filizoğlu, S. Kesim, et al.(2021) "Physiological Biodistribution of (68)Ga-DOTA-TATE in Normal Subjects." Review of Mol Imaging Radionucl Ther. 30, no. (1): 39-46. https://doi.org/https://doi.org/10.4274/mirt.galenos.2021.37268.
53. Hofman, M.S., W.F. Lau, and R.J. Hicks.(2015) "Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation." Review of Radiographics. 35, no. (2): 500-16. https://doi.org/https://doi.org/10.1148/rg.352140164.
54. Boughdad S, M.M., Prior OJ.(2021) "Prevalence of physiological uptake in the pancreas on somatostatin receptor-based PET/CT: a systematic review and a meta-analysis." Review of Clinical and Translational Imaging. no.
55. Brabander, T., J. Teunissen, and D. Kwekkeboom.(2017) "Physiological Uptake in the Pancreatic Head on Somatostatin Receptor Scintigraphy Using [111In-DTPA]Octreotide: Incidence and Mechanism." Review of Clin Nucl Med. 42, no. (1): 15-19. https://doi.org/https://doi.org/10.1097/rlu.0000000000001431.
56. Beauregard, J.M., M.S. Hofman, G. Kong, et al.(2012) "The tumour sink effect on the biodistribution of 68Ga-DOTA-octreotate: implications for peptide receptor radionuclide therapy." Review of Eur J Nucl Med Mol Imaging. 39, no. (1): 50-6. https://doi.org/https://doi.org/10.1007/s00259-011-1937-3.
57. Vertenten, B., L. Goethals, and F. De Geeter.(2019) "(68)Ga DOTATATE Uptake in Hemangioma Simulating Metastasis on PET Imaging: CT helps characterize bone hemangioma that could be wrongly interpreted as skeletal metastases on (68)Ga DOTATATE PET imaging." Review of J Belg Soc Radiol. 103, no. (1): 38. https://doi.org/https://doi.org/10.5334/jbsr.1772.
58. Kohlenberg, J.D., A. Panda, G.B. Johnson, et al.(2021) "Radiologic and clinicopathologic characteristics of thyroid nodules with focal 68Ga-DOTATATE PET activity." Review of Nucl Med Commun. 42, no. (5): 510-516. https://doi.org/https://doi.org/10.1097/mnm.0000000000001356.
59. Garin, E., F. Le Jeune, A. Devillers, et al.(2009) "Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors." Review of J Nucl Med. 50, no. (6): 858-64. https://doi.org/https://doi.org/10.2967/jnumed.108.057505.
60. Bahri, H., L. Laurence, J. Edeline, et al.(2014) "High prognostic value of 18F-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation." Review of J Nucl Med. 55, no. (11): 1786-90. https://doi.org/https://doi.org/10.2967/jnumed.114.144386.
61. Binderup, T., U. Knigge, C.B. Johnbeck, et al.(2021) "(18)F-FDG PET is Superior to WHO Grading as a Prognostic Tool in Neuroendocrine Neoplasms and Useful in Guiding PRRT: A Prospective 10-Year Follow-up Study." Review of J Nucl Med. 62, no. (6): 808-815. https://doi.org/https://doi.org/10.2967/jnumed.120.244798.

62. Nilica, B., D. Waitz, V. Stevanovic, et al.(2016) "Direct comparison of (68)Ga-DOTA-TOC and (18)F-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle." Review of Eur J Nucl Med Mol Imaging. 43, no. (9): 1585-92. https://doi.org/https://doi.org/10.1007/s00259-016-3328-2.
63. Binderup, T., U. Knigge, A. Loft, et al.(2010) "18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors." Review of Clin Cancer Res. 16, no. (3): 978-85. https://doi.org/https://doi.org/10.1158/1078-0432.Ccr-09-1759.
64. Carideo, L., D. Prosperi, F. Panzuto, et al.(2019) "Role of Combined [(68)Ga]Ga-DOTA-SST Analogues and [(18)F]FDG PET/CT in the Management of GEP-NENs: A Systematic Review." Review of J Clin Med. 8, no. (7). https://doi.org/https://doi.org/10.3390/jcm8071032.
65. Chan, D.L., N. Pavlakis, G.P. Schembri, et al.(2017) "Dual Somatostatin Receptor/FDG PET/CT Imaging in Metastatic Neuroendocrine Tumours: Proposal for a Novel Grading Scheme with Prognostic Significance." Review of Theranostics. 7, no. (5): 1149-1158. https://doi.org/https://doi.org/10.7150/thno.18068.
66. Bailey, D., D. Chan, P. Roach, et al.(2019) "The Prognostic Impact of Dual FDG/Somatostatin Receptor PET in Metastatic Neuroendocrine Tumours: Updated Overall Survival from the NETPET Study." Review of Journal of Nuclear Medicine. 60, no. (supplement 1): 505-505.
67. Lee, H., R. Nakamoto, S.E. Moore, et al.(2021) "Combined Quantification of (18)F-FDG and (68)Ga-DOTATATE PET/CT for Prognosis in High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms." Review of Acad Radiol. no. https://doi.org/https://doi.org/10.1016/j.acra.2021.10.004.
68. Montravers, F., K. Kerrou, V. Nataf, et al.(2009) "Impact of fluorodihydroxyphenylalanine-18F positron emission tomography on management of adult patients with documented or occult digestive endocrine tumors." Review of J Clin Endocrinol Metab. 94, no. (4): 1295-301. https://doi.org/https://doi.org/10.1210/jc.2008-1349.
69. Balogova, S., J.N. Talbot, V. Nataf, et al.(2013) "18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type." Review of Eur J Nucl Med Mol Imaging. 40, no. (6): 943-66. https://doi.org/https://doi.org/10.1007/s00259-013-2342-x.
70. Ansquer, C., Y. Touchefeu, A. Faivre-Chauvet, et al.(2021) "Head-to-Head Comparison of 18F-DOPA PET/CT and 68Ga-DOTANOC PET/CT in Patients With Midgut Neuroendocrine Tumors." Review of Clin Nucl Med. 46, no. (3): 181-186. https://doi.org/https://doi.org/10.1097/rlu.0000000000003450.
71. Ouvrard, E., E. Chevalier, P. Addeo, et al.(2021) "Intraindividual comparison of (18) F-FDOPA and (68) Ga-DOTATOC PET/CT detection rate for metastatic assessment in patients with ileal neuroendocrine tumours." Review of Clin Endocrinol (Oxf). 94, no. (1): 66-73. https://doi.org/https://doi.org/10.1111/cen.14312.
72. Veenstra, E.B., D.J.A. de Groot, A.H. Brouwers, et al.(2021) "Comparison of 18F-DOPA Versus 68Ga-DOTATOC as Preferred PET Imaging Tracer in Well-Differentiated Neuroendocrine Neoplasms." Review of Clin Nucl Med. 46, no. (3): 195-200. https://doi.org/https://doi.org/10.1097/rlu.0000000000003447.
73. Imperiale, A., E. Rust, S. Gabriel, et al.(2014) "18F-fluorodihydroxyphenylalanine PET/CT in patients with neuroendocrine tumors of unknown origin: relation to tumor origin and differentiation." Review of J Nucl Med. 55, no. (3): 367-72. https://doi.org/https://doi.org/10.2967/jnumed.113.126896.
74. Antwi, K., M. Fani, T. Heye, et al.(2018) "Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study." Review of Eur J Nucl Med Mol Imaging. 45, no. (13): 2318-2327. https://doi.org/https://doi.org/10.1007/s00259-018-4101-5.
75. Luo, Y., Q. Pan, S. Yao, et al.(2016) "Glucagon-Like Peptide-1 Receptor PET/CT with 68Ga-NOTA-Exendin-4 for Detecting Localized Insulinoma: A Prospective Cohort Study." Review of J Nucl Med. 57, no. (5): 715-20. https://doi.org/https://doi.org/10.2967/jnumed.115.167445.
76. Andreassen, M., E. Ilett, D. Wiese, et al.(2019) "Surgical Management, Preoperative Tumor Localization, and Histopathology of 80 Patients Operated on for Insulinoma." Review of J Clin Endocrinol Metab. 104, no. (12): 6129-6138. https://doi.org/https://doi.org/10.1210/jc.2019-01204.
77. Prasad, V., A. Sainz-Esteban, R. Arsenic, et al.(2016) "Role of (68)Ga somatostatin receptor PET/CT in the detection of endogenous hyperinsulinaemic focus: an explorative study." Review of Eur J Nucl Med Mol Imaging. 43, no. (9): 1593-600. https://doi.org/https://doi.org/10.1007/s00259-016-3331-7.
78. Falconi, M., B. Eriksson, G. Kaltsas, et al.(2016) "ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors." Review of Neuroendocrinology. 103, no. (2): 153-71. https://doi.org/https://doi.org/10.1159/000443171.
79. Fani, M., G.P. Nicolas, and D. Wild.(2017) "Somatostatin Receptor Antagonists for Imaging and Therapy." Review of J Nucl Med. 58, no. (Suppl 2): 61s-66s. https://doi.org/https://doi.org/10.2967/jnumed.116.186783.
80. Nicolas, G.P., N. Schreiter, F. Kaul, et al.(2018) "Sensitivity Comparison of (68)Ga-OPS202 and (68)Ga-DOTATOC PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors: A Prospective Phase II Imaging Study." Review of J Nucl Med. 59, no. (6): 915-921. https://doi.org/https://doi.org/10.2967/jnumed.117.199760.
81. Pauwels, E., F. Cleeren, T. Tshibangu, et al.(2020) "[(18)F]AlF-NOTA-octreotide PET imaging: biodistribution, dosimetry and first comparison with [(68)Ga]Ga-DOTATATE in neuroendocrine tumour patients." Review of Eur J Nucl Med Mol Imaging. 47, no. (13): 3033-3046. https://doi.org/https://doi.org/10.1007/s00259-020-04918-4.
82. Long, T., N. Yang, M. Zhou, et al.(2019) "Clinical Application of 18F-AlF-NOTA-Octreotide PET/CT in Combination With 18F-FDG PET/CT for Imaging Neuroendocrine Neoplasms." Review of Clin Nucl Med. 44, no. (6): 452-458. https://doi.org/https://doi.org/10.1097/rlu.0000000000002578.
83. Hou, J., T. Long, Z. He, et al.(2021) "Evaluation of (18)F-AlF-NOTA-octreotide for imaging neuroendocrine neoplasms: comparison with (68)Ga-DOTATATE PET/CT." Review of EJNMMI Res. 11, no. (1): 55. https://doi.org/https://doi.org/10.1186/s13550-021-00797-4.