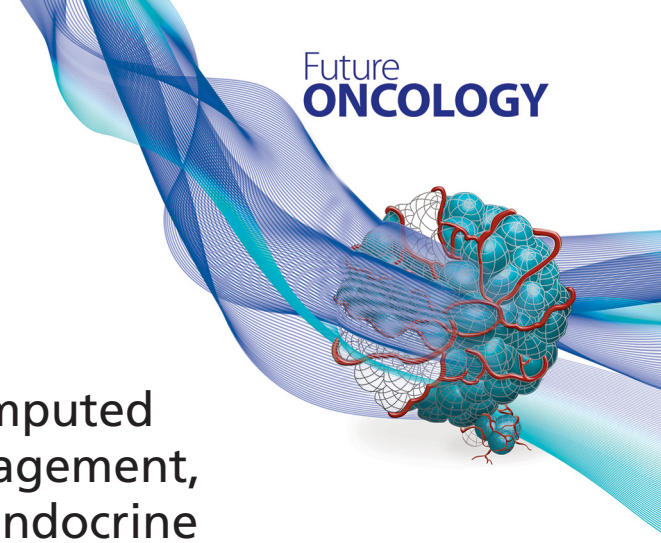
Drug Evaluation



The utility of ^{68}Ga-DOTATATE positron-emission tomography/computed tomography in the diagnosis, management, follow-up and prognosis of neuroendocrine tumors

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Neuroendocrine tumors (NETs) are rare neoplasms that emerge mainly from the GI tract, pancreas and respiratory tract. The incidence of NETs has increased more than sixfold in the last decades. NETs typically express somatostatin receptors on their cell surface, which can be targeted by 'cold' somatostatin analogs for therapy or by 'hot' radiolabeled somatostatin analogs for tumor localization and treatment. 68-Gallium-DOTA peptides (DOTATATE, DOTATOC, DOTANOC) positron emission tomography/computed tomography is a highly accurate imaging modality for NETs that has been found to be more sensitive for NET detection than other imaging modalities. In the current review, we will discuss the clinical utility of 68-Gallium-DOTATATE positron emission tomography/computed tomography for the diagnosis and management of patients with NETs.

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Keywords: ^{68}Ga-DOTATATE • diagnosis • management • neuroendocrine tumors • PET

Background

Neuroendocrine tumors (NETs) are a group of neoplasms originating from neuroendocrine cells, located mainly in the GI and respiratory tracts. A recent report showed a more than sixfold increase in the incidence of NETs in the last decades, reaching 6.4 new cases of NETs per 100,000 inhabitants per year in the USA [1]. NETs can be subclassified based on the WHO's tumor grade classification system according to the extent of the disease (localized, regional or metastatic) and based on three additional factors: the Ki-67 labeling index and mitotic rates [2], the functional status of the tumors (secreting substances that cause clinical syndromes vs nonfunctional) and whether the NETs are sporadic or part of a hereditary syndrome.

NETs typically express somatostatin receptors (SSTRs) on their cell membranes. Of the five known SSTR subtypes, the two most commonly expressed in NETs are subtypes 2a and 5 [3]. This has clinical importance for NET management. First, patients with functional or unresectable NETs can be treated by targeting the tumors with 'cold' somatostatin analogs – octreotide [4], lanreotide [5] and pasireotide [6] – that alleviate some symptoms associated with functional NETs and increase progression-free survival. The use of 'hot', or radiolabeled, somatostatin analogs for patients with NETs has been shown to be useful for disease detection with both single-photon emission computed tomography (SPECT)/computed tomography (CT) and positron-emission tomography (PET)/CT. 68-Gallium (^{68}Ga)-DOTA peptides (DOTATATE [7], DOTATOC [8], DOTANOC [9]) PET/CT is a highly accurate imaging modality for NET detection. SSTRs in NETs can also be targeted with radioisotope therapy, referred to as peptide-receptor radionuclide therapy (PRRT). In the recently published NETTER-1 prospective randomized controlled trial, treatment with PRRT and octreotide improved both progression-free survival and overall survival in patients with advanced, well-differentiated midgut NETs compared with patients only receiving octreotide therapy [10].

Future Medicine

Table 1. Sensitivity and specificity of functional and anatomical imaging modalities for neuroendocrine tumors of different sites.

	GEP-NET [Ref.]	Bronchial NET [Ref.]	Liver metastases [Ref.]	Bone metastases [Ref.]
^{68}Ga-DOTA peptides PET/CT	82–100/88–100 [24–31]	81–96/100[‡] [32–35]	74–96/88–100 [31,36–37]	75–100/89–100 [31,38–40]
^{18}F-FDG PET/CT	26–66/100 [24,31]	54–78/11[†] [32,34,41–42]	55–70/100 [31,43]	75/100 [31]
CT	90/90 [27,44]	NA[‡]	75–100/83–95 [27,44–45]	47–80/49–98 [27,38,40]
MRI	98/90 [27]	NA	80–98/97–100 [46,47]	76/94 [27]

[‡] The accuracy of functional imaging in identifying NETs differs according to tumor type and grade. For example, when separating pulmonary NETs into typical and atypical classifications, ^{18}F-FDG PET/CT had a sensitivity of 61.9 and 100%, while ^{68}Ga-DOTATATE PET/CT had an inverse pattern, with sensitivity of 100 and 80%, respectively [32].
[†] Forty percent of pulmonary NETs are incidentally identified by CT, often with nonspecific appearance but with typical enhancement in the early arterial phase [48].
^{18}F-FDG: ^{18}F-fluorodeoxyglucose; CT: Computed tomography; GEP-NET: Gastroenteropancreatic neuroendocrine tumor; NET: Neuroendocrine tumor; PET: Positron emission tomography.
Data taken from [12,23,49–51].

In this focused review, we describe the basic characteristics of ^{68}Ga-DOTATATE PET/CT, an SSTR-based functional imaging modality, and address its use in diagnosis, management and precision medicine for patients with NETs.

Development of ^{68}Ga-DOTATATE PET/CT & basic radiopharmaceutical characteristics

Radiolabeled SSTR-binding molecules are used regularly for NET imaging. The first somatostatin analog-based tracer used to localize NET was octreotide, which was labeled with 123-Iodine [11]. Somatostatin receptor scintigraphy (SRS) with ^{111}In-DTPA-octreotide (OctreoScan^{TM}) was the mainstay for this purpose for many decades [12], but it has been replaced by the ^{68}Ga-labeled DOTA peptide somatostatin analogs. These include ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC, all of which are radiolabeled derivatives of the somatostatin analog octreotide. The ^{68}Ga-DOTA molecules can be used for PET/CT imaging and have several advantages over SRS, making it the imaging method of choice for NETs [13]. These advantages include higher sensitivity of ^{68}Ga-DOTA peptide-based PET/CT versus SRS for NET localization [7,14–16] (mainly explained by the higher spatial resolution of PET vs SRS), less time required to complete the scan (1 vs 24 h or more, respectively) [17] and lower radiation dose per scan [18].

In addition to the uptake of ^{68}Ga-DOTATATE in NET cells, there is also a physiological uptake in some organs. Those organs with high uptake include the spleen, adrenal glands, kidneys and pituitary gland, and those with moderate uptake include the liver, thyroid and salivary glands [17,19]. The physiological uptake can be explained, in part, by the expression of SSTRs in these organs, (e.g., pituitary and thyroid glands) or by nonspecific tracer absorption in other organs. The ratio of the tracer uptake by the NET to the background physiological uptake in normal tissues is another measure for the tumor detection capability of a tracer. The ratios differ between the various organs depending on their physiological uptake. The tumor-to-liver maximum standardized uptake value (SUVmax) ratios between the different ^{68}Ga-DOTA peptides are comparable, with a tumor-to-liver SUVmax ratio of 3.4 for ^{68}Ga-DOTANOC [20], 2.8 for ^{68}Ga-DOTATOC [21] and 2.8 for ^{68}Ga-DOTATATE [19]. Another important technical issue is the effect of concomitant treatment with 'cold' somatostatin analogs on the accuracy of SSTR-based PET/CT. Somatostatin analogs may affect both physiological ^{68}Ga-DOTATATE uptake and tracer uptake by tumor cells [22]. Hence, before performing a scan, patients should hold treatment with short-acting somatostatin analogs for 24 h and perform the scan 1 week prior to the next scheduled injection of long-acting somatostatin analogs (when administered monthly) [17].

^{68}Ga-DOTATATE PET/CT in NET diagnosis

The sensitivity and specificity of ^{68}Ga-DOTA peptides-based imaging as well as conventional imaging modalities for NETs of various sites are detailed in Table 1. In a systematic review including 22 studies, ^{68}Ga-DOTA peptide-based PET/CT had an excellent diagnostic accuracy, with an area under the receiver operating characteristic curve of 0.98 for identifying NETs and a sensitivity and specificity of 93 and 96%, respectively [23].

The utility of ^{68}Ga-DOTATATE for the diagnosis of NETs was shown by several groups [7,38] who demonstrated its superiority over both anatomical (CT and MRI) and functional imaging modalities (^{18}F-fluorodeoxyglucose [^{18}F-FDG] PET/CT and Octreoscan). Furthermore, in a meta-analysis of ten studies in patients with NETs, ^{68}Ga-DOTATATE was found to be more specific compared with ^{68}Ga-DOTATOC PET [49]. The high sensitivity of ^{68}Ga-DOTA peptides-based PET/CT is especially important for identifying patients with a metastatic NET of

unknown origin, when other imaging modalities do not localize the primary tumor site. This has been shown for ^{68}Ga-DOTATATE PET/CT, which identified the primary tumor site in 4 of 14 (28.6%) patients with a previously unknown primary lesion [7], and for ^{68}Ga-DOTANOC PET/CT [52], which had a reported detection rate of 59% (34/59 patients).

SSTR-based PET/CT was reported to have a high sensitivity in patients with malignant insulinomas [17,53] but a relatively low sensitivity in patients with benign tumors [17]. This was explained by the relatively low expression of SSTR type 2 in those tumors not detected [54]. However, ^{68}Ga-DOTATATE PET/CT has been found to be useful for locating small functional NETs and has shown a high sensitivity for detecting insulinomas, with the lesions identified in 9 of 10 patients [55].

Thoracic NETs comprise a heterogeneous group of tumors ranging from benign typical carcinoids to atypical carcinoids and the highly aggressive and poorly differentiated small- and large-cell neuroendocrine carcinomas [56]. Seventy percent of pulmonary NETs express SSTR type 1 and 2, with the highest density expressing the type 2 receptors [54]. The high affinity of ^{68}Ga-DOTATATE for SSTR type 2 makes it a favorable tracer for these tumors. However, SSTR-based PET/CT was found to be less useful in intermediate and high-grade pulmonary NETs as compared with ^{18}F-FDG PET/CT. Among patients with low-grade tumors, a comparable sensitivity was found between PET/CT scans using ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE [50].

In addition to its superior accuracy for detecting NETs and thus altering patient management, ^{68}Ga-DOTATATE PET/CT can be used as an accurate tool for assessing total disease burden. This can be achieved with PET scans using semiautomatic computed techniques [57]. We have evaluated the utility of measuring ^{68}Ga-DOTATATE-avid tumor volumes in patients with NETs by using an SUVmax threshold segmentation method [58], which allowed us to assess the utility of different biochemical biomarkers for measuring disease burden. This was also true among patients with hereditary syndromes (multiple endocrine neoplasia syndrome type 1, von Hippel–Lindau disease, Figure 1).

The CT protocol recommended for ^{68}Ga-DOTA peptide-based PET/CT includes three components: a topogram, a low-dose scan used for attenuation correction and a triple-phase CT with intravenous contrast injection [12]. A study analyzing the CT components of ^{68}Ga-DOTATATE PET/CT [59] compared the diagnostic accuracy of the arterial, portal venous and venous phases of the CT scan, both separately and as a combined triple-phase CT scan, with the PET component. Although the PET component was found to be the most accurate, the triple-phase CT scan provided useful anatomical information and exclusively demonstrated lesions via the different CT-scan phases, which justifies the use of a standard triple-phase CT.

The combination of ^{68}Ga-DOTA-based PET with MRI may further increase imaging accuracy for patients with NETs. A pilot study comparing ^{68}Ga-DOTATOC PET/CT versus PET/MRI showed a potential benefit for the latter in the detection of liver metastases [60]. In another study, ^{68}Ga-DOTATOC PET/MRI demonstrated a higher sensitivity for detecting NETs overall as well as for detecting liver NET metastases compared with ^{68}Ga-DOTATOC PET/CT. However, ^{68}Ga-DOTATOC PET/MRI was inferior to PET/CT for detecting bone and lung NET metastases [61].

^{68}Ga-DOTATATE PET/CT for tailoring NET management

The central role of ^{68}Ga-DOTA-based PET/CT in the diagnosis and management of patients with NET is reflected by the clinical guidelines for the management of NET, which indicate their use for the detection and follow-up of well-differentiated NETs in any anatomic location [12,15,48,56,62–67]. In Figure 2, we summarized the recommendations for imaging modality selection for NETs of various anatomical sites, grades and stages based on the guidelines of the European Neuroendocrine Tumors Society and the European Society of Medical Oncology. ^{68}Ga-DOTATATE PET/CT imaging impacts the management of patients with NETs. Hofman *et al.* [68] showed that ^{68}Ga-DOTATATE PET/CT leads to changes in treatment modality in 47% of patients (n = 59) by identifying lesions that are candidates for resection or by identifying multiple unresectable lesions, which leads to systemic therapy initiation over surgical intervention. We have shown, in a prospective study of patients with gastroenteropancreatic NETs, that ^{68}Ga-DOTATATE PET/CT results also changed the management of 43 of 131 patients (32.8%) [7] by identifying additional lesions as compared with SRS and CT scans.

SSTR-based PET/CT has been shown to be useful in the management of NETs in patients with hereditary syndromes. In patients with multiple endocrine neoplasia syndrome type 1, both ^{68}Ga-DOTATOC PET/CT [69] and ^{68}Ga-DOTATATE PET/CT were shown to be superior to SRS for detecting NETs, suggesting that this

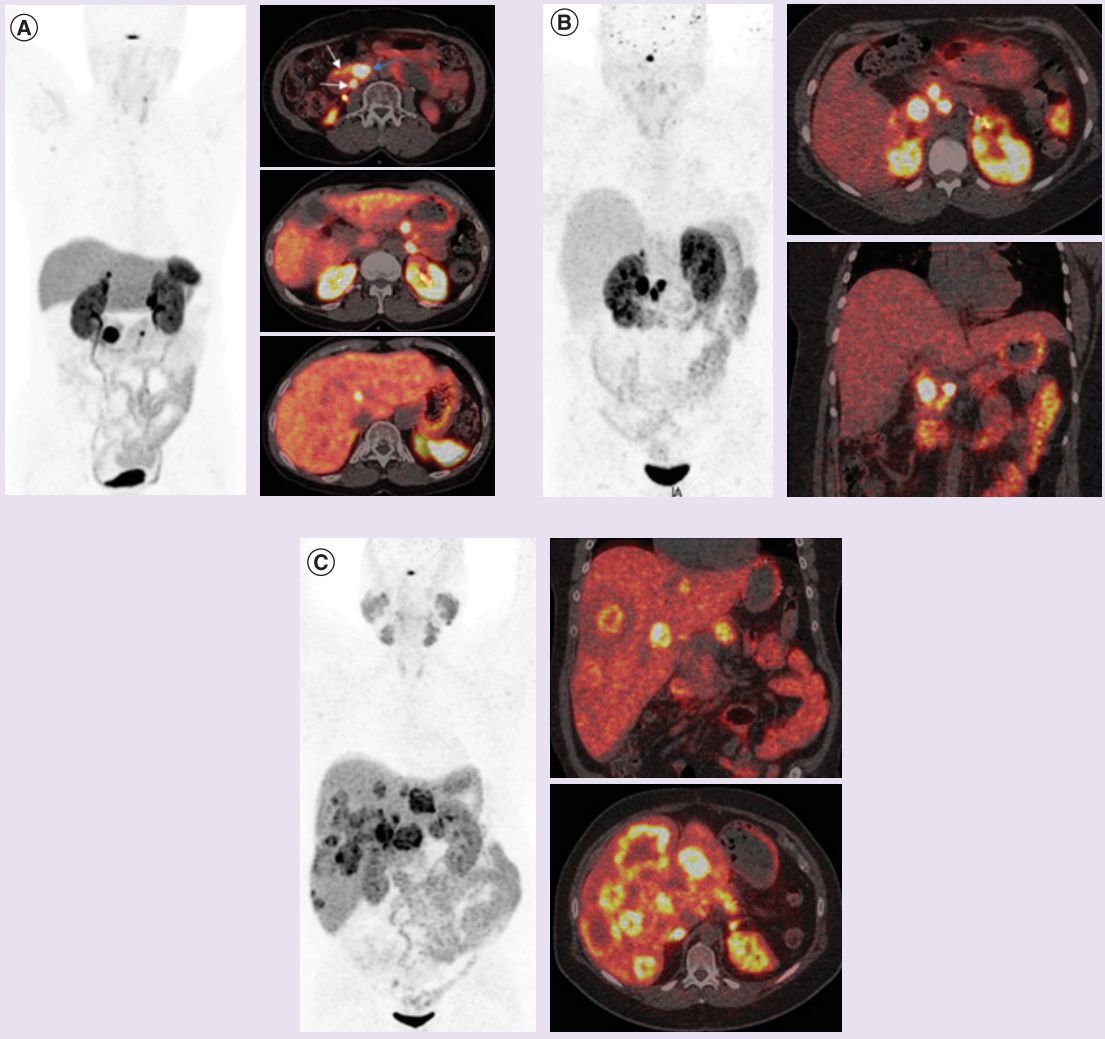

Figure 1. The utility of ^{68}Ga-DOTATATE positron-emission tomography/computed tomography scans in patients with hereditary syndromes. A multiple endocrine neoplasia syndrome type 1 patient with a gastrinoma located in the pancreas (blue arrow) and duodenum (white arrows) and one liver metastasis **(A)**, and two patients with von Hippel–Lindau disease with multiple pancreatic NETs **(B)** and pancreatic NETs metastatic to the liver **(C)**. The figures on the left **(A–C)** are maximal image projections of ^{68}Ga-DOTATATE PET. All figures on the right in **(A)**, the upper right in **(B)** and the lower right in **(C)** are transverse ^{68}Ga-DOTATATE PET/CT-fusion images. Those on the lower right in B and upper right in **(C)** are coronal ^{68}Ga-DOTATATE PET/CT-fusion images.
CT: Computed tomography; NET: Neuroendocrine tumor; PET: Positron-emission tomography.

modality could be adapted for screening and/or surveillance [70]. In patients with von Hippel–Lindau disease, ^{68}Ga-DOTATOC PET/CT detected a higher proportion of pancreatic NETs than SRS [71].

^{68}Ga-DOTATATE PET/CT utility for follow-up & prognosis prediction

PRRT is an important modality used for treating patients with SSTR-expressing NETs. Since the treatment is based on SSTR expression, it is necessary to demonstrate the avidity of the tumor to SSTR-based tracers in order to determine patient eligibility for PRRT [12,72]. Baseline ^{68}Ga-DOTATATE PET/CT characteristics have been evaluated as prognostic factors for PRRT outcome in patients with NET, with several PET parameters suggested for this aim including tracer uptake by the tumor, measurement by SUVmax (Figure 3) [73], and tumor-to-liver and tumor-to-spleen SUVmax ratios [73]. In addition, textural tumor features resembling intratumoral SSTR heterogeneity can be computed and have been found to be superior to the aforementioned conventional parameters for predicting the survival of patients with NETs [74]. Repeated ^{68}Ga-DOTATATE PET/CT scans have also

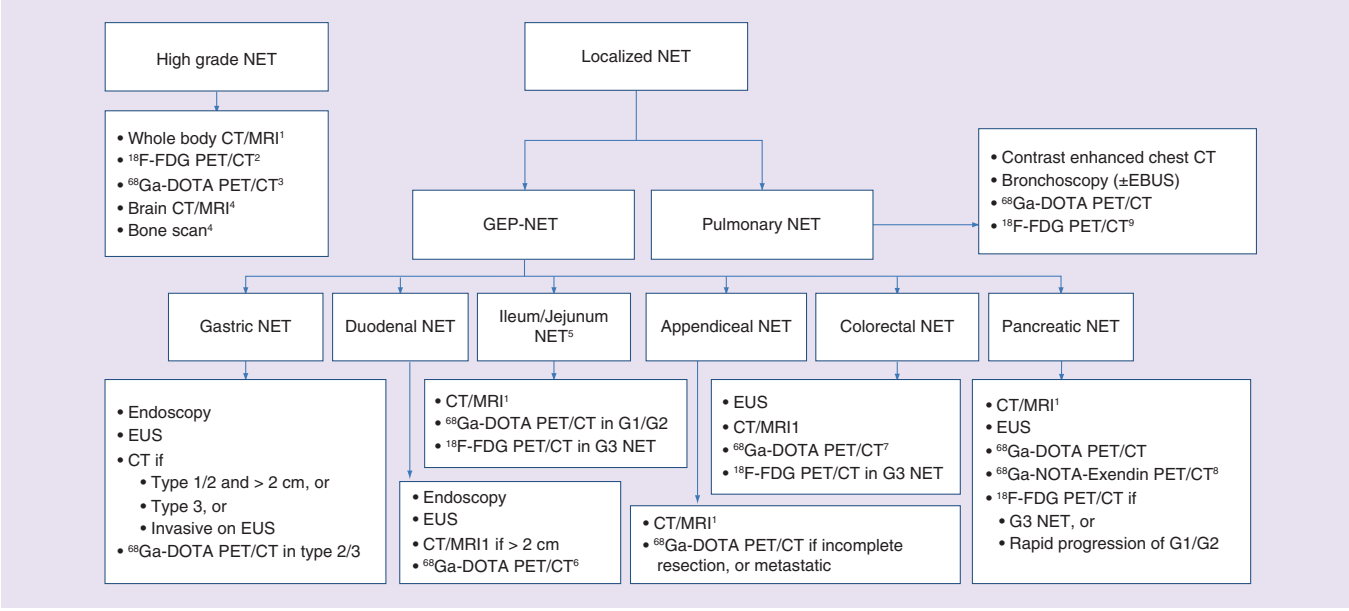

Figure 2. Algorithm for the recommended use of different imaging modalities for neuroendocrine tumors, according to the site of the primary lesion, based on current guidelines. G1, G2 and G3 are tumor grades according to the WHO's classification for neuroendocrine tumors. ^{111}In-pentetreotide single-photon emission computed tomography/CT is an optional substitute for ^{68}Ga-DOTA-based PET/CT if the latter is not available. However, its accuracy in NET diagnosis is inferior to ^{68}Ga-DOTA-based PET/CT [7].
[1]Three-phase, contrast-enhanced CT and/or contrast-enhanced MRI.
[2]If candidate for surgery, or if findings in anatomical imaging are equivocal.
[3]Only in G3 with Ki-67 <55%.
[4]Only if clinically indicated.
[5]For NET of unknown primary site, add capsule endoscopy, CT (or MRI) enteroclysis, double-balloon enteroscopy or colonoscopy.
[6]If metastatic and/or >2 cm.
[7]If lesion >2 cm and/or G3.
[8]For detecting insulinoma.
[9]If atypical carcinoid or high grade.
CT: Computed tomography; EBUS: Endobronchial ultrasound; EUS: Endoscopic ultrasound; FDG: Fluorodeoxyglucose; GEP-NET: Gastroenteropancreatic NET; NET: Neuroendocrine tumor; PET: Positron emission tomography.
Data taken from [12,15,48,56].

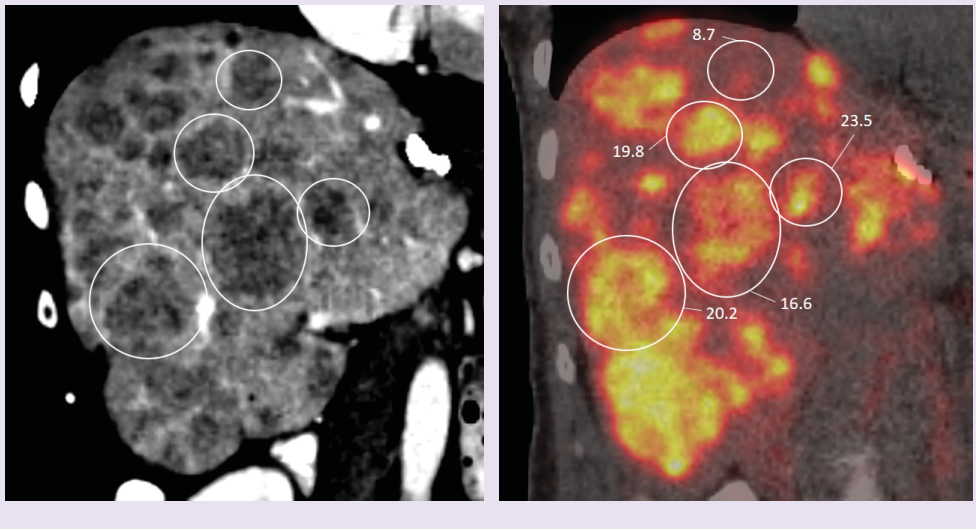

Figure 3. A patient with a metastatic neuroendocrine tumor of unknown primary site. Contrast-enhanced computed tomography scan (left) with selected liver metastases encircled and the corresponding fusion image of ^{68}Ga-DOTATATE positron emission tomography/computed tomography (right) showing the heterogeneous ^{68}Ga-DOTATATE avidity. Numbers represent maximal standardized uptake value per lesion.

proved useful for tailoring patient management, as a decrease in the ^{68}Ga-DOTATATE tumor-to-spleen SUV ratio following PRRT was associated with a lower risk of disease progression [75]. However, due to high variability between examinations, the use of spleen SUV as a denominator weakens the reliability of this measure.

Several retrospective studies have assessed radiolabeled SSTR-binding ligands as prognostic markers for NETs. In these studies, a low SUVmax was reported to be associated with poor prognosis in patients with NETs [76–78]. This can be explained by the lower expression of SSTRs in tumors that are poorly differentiated and have a higher grade. Another important determinant for NET patient prognosis is disease grade, which can be reflected in ^{18}F-FDG uptake (see the detailed discussion below in 'Dual-tracer PET/CT').

In addition to the conventional PET parameters, computational tools that will enable automatic or semiautomatic measurement of disease burden based on ^{68}Ga-DOTATATE-avid tumor volume might enable us to better predict disease outcomes. In a prospective study of patients with gastroenteropancreatic NETs, high total tumor volumes were associated with a higher risk for disease progression and for disease-specific mortality based on a semiautomatic ^{68}Ga-DOTATATE-avidity-based measurement [79].

Dual-tracer PET/CT

NET grade, as determined by the proliferative index Ki-67 and the mitotic rate, is an independent predictor of prognosis [80]. Low-grade tumors are usually moderately or well differentiated and, hence, express SSTRs on their cell membrane. High-grade tumors, especially neuroendocrine carcinomas, originate from poorly differentiated cells, commonly have low or absent SSTR expression and tend to have higher glycolytic and metabolic rates (Figure 4) [24].

The tumor biology characteristics of NETs can be demonstrated in a noninvasive way by performing PET/CT using two different tracers: ^{18}F-FDG for measuring the tumor metabolic rate and ^{68}Ga-DOTA peptide-based tracer for demonstrating the expression of SSTRs. The combined use of these two tracer types is known as dual-tracer PET/CT. When the utility of the two tracers was compared across NETs of gastrointestinal origin and of different grades, ^{68}Ga-DOTATATE was found to be superior to ^{18}F-FDG in patients with low-grade tumors. However, in patients with high-grade NETs, tumor assessment was found to be more comprehensive when the two ligands were integrated [24]. The combined use of ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT slightly improved the accuracy of ^{68}Ga-DOTATATE PET/CT alone in patients with pancreatic NETs, although it did not change the disease management [81]. However, dual-tracer PET/CT has been shown to be helpful in characterizing pulmonary NETs, with atypical and high-grade pulmonary NETs showing less ^{68}Ga-DOTATATE and more ^{18}F-FDG avidity and with an inverse pattern among typical, low-grade and well-differentiated tumors [82]. In addition to its use in tumor characterization, ^{18}F-FDG uptake by NETs has also been shown to have prognostic significance. NETs with high ^{18}F-FDG avidity (SUVmax greater than 3) were independently associated with a higher risk for disease progression [83].

A noninvasive method to assess tumor grade and – by proxy – tumor aggressiveness is especially important in patients with advanced NETs. Metastatic NETs have both intra- and intertumoral heterogeneity in terms of tumor grade, both between the primary lesion and the metastases and between different metastatic lesions [84]. Hence, a single-lesion biopsy has a high risk of missing the lesion of the highest grade, possibly leading to an inaccurate assessment of the patient's risk and an improper management plan. Whole-body dual-tracer PET/CT has the advantage of characterizing the full extent of the disease. Based on this characterization, high-risk lesions, namely those with higher ^{18}F-FDG and lower ^{68}Ga-DOTATATE avidity, can be selected for biopsy with potentially better diagnostic accuracy of the extent of the disease and the likely tumor biology.

The dual-tracer PET/CT was also suggested as a tool for determining the potential benefit that a patient with NET may receive from treatment with PRRT. Chan *et al.* [85] performed a retrospective study of patients with metastatic NETs that underwent both SSTR-based and ^{18}F-FDG PET/CT scans, and they developed a score (the 'NETPET score') based on the lesion uptake of the different tracers. The score was associated with patients' survival in a multivariable analysis.

In summary, ^{68}Ga-DOTATATE PET/CT has emerged as a highly accurate imaging method for patients with NETs. It is useful not only for identifying the tumors but also as a theranostic tool for stratifying each patient's risk and assessing the response to treatment. Developing computed techniques for ^{68}Ga-DOTATATE PET/CT interpretation in the future will further extend the utility of this robust clinical tool for the management of patients with NETs.

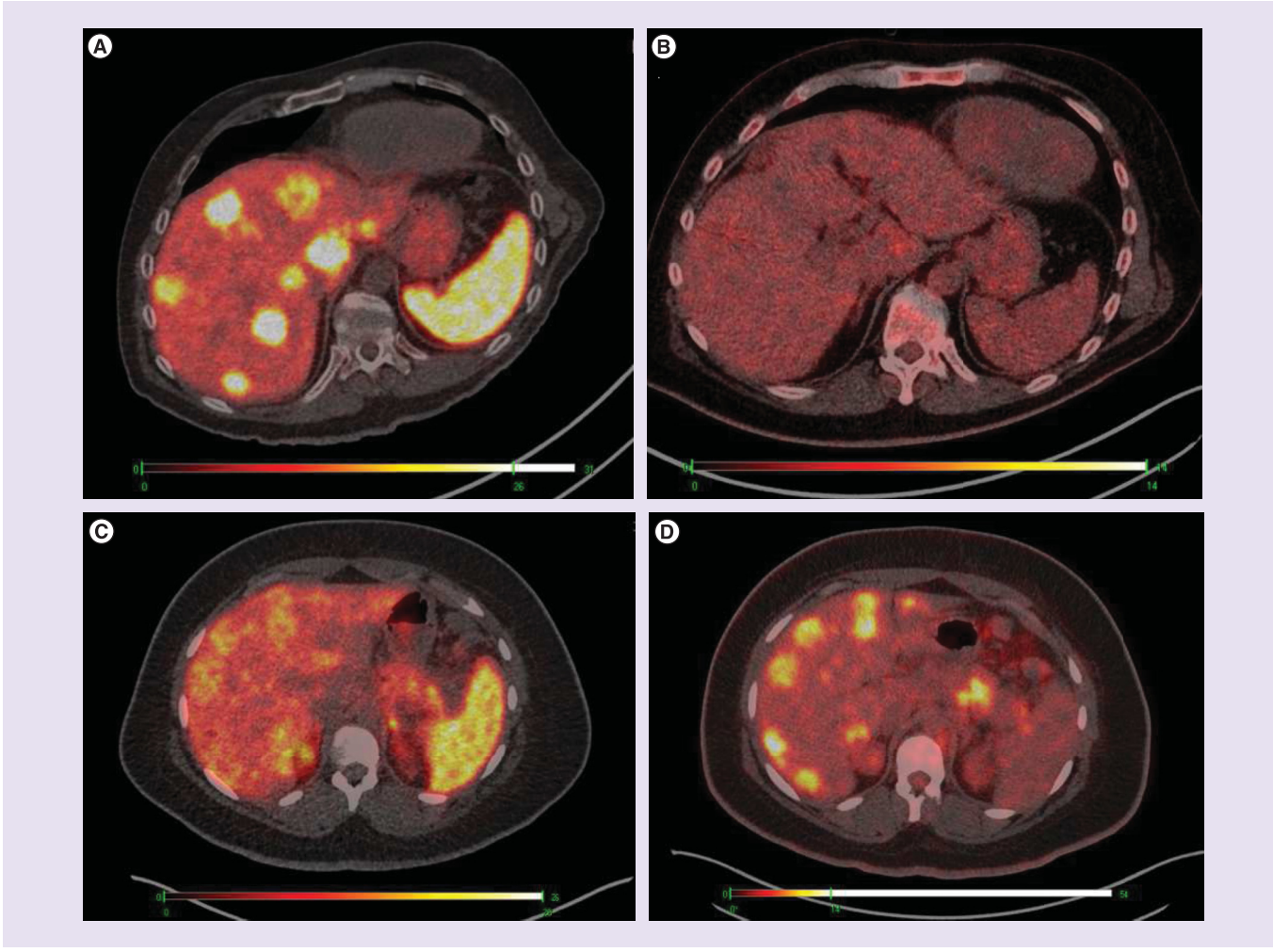

Figure 4. The utility of dual-tracer imaging. Positron emission tomography/computed tomography scans of a patient with a metastatic grade 1 neuroendocrine tumor showing a high ^{68}Ga-DOTATATE uptake and a low ^{18}F-fluorodeoxyglucose uptake (**A & B**, respectively), and scans of a patient with a metastatic grade 3 neuroendocrine tumor showing a heterogeneous uptake of ^{68}Ga-DOTATATE and a high uptake of ^{18}F-fluorodeoxyglucose (**C & D**, respectively).

Conclusion

The use of different ligands will be widened significantly. In the future, we anticipate that patients with NETs will undergo multiple imaging studies using several ligands, facing the low radiation dose required for PET/CT scanning. This will enable a noninvasive characterization of the tumor biology and predicted disease course. We predict, based on data that will emerge in the coming years, that this will enable patient-specific treatment management using specific medical agents and radiolabeled peptides. Moreover, simple one-step analysis of the scans will enable immediate and accurate risk stratification as well as the identification of patients who may benefit from intervention versus those who may be followed expectantly and would benefit from less treatment adverse effects.

Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

Executive summary

Background: neuroendocrine tumors

- Neuroendocrine tumors (NETs) typically express somatostatin receptors (SSTRs) on their cell membrane.
- SSTRs can be targeted using somatostatin analogs for conventional medical therapy.
- Radiolabeled somatostatin analogs can be used for functional imaging and targeted therapy.

Development of ^{68}Ga-DOTATATE positron emission tomography/computed tomography & basic radiopharmaceutical characteristics

- Radiolabeled SSTR-binding molecules are used regularly for the imaging of NETs, mainly using ^{68}Ga-labeled somatostatin analogs including ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC.
- Treatment with short-acting somatostatin analogs should be held for 24 h before performing the scan, and the scan should be performed one week before the next scheduled injection of long-acting somatostatin analogs (when administered monthly).

^{68}Ga-DOTATATE positron emission tomography/computed tomography in NET diagnosis

- ^{68}Ga-DOTATATE has high sensitivity and specificity for the diagnosis of NETs compared with other anatomical/functional imaging modalities, especially in low-grade, moderately differentiated and well-differentiated NETs.
- The high sensitivity of ^{68}Ga-DOTATATE positron emission tomography/computed tomography (PET/CT) is especially important for identifying patients with metastatic NETs of unknown origin.
- ^{68}Ga-DOTATATE PET/CT was found to be useful for locating insulinomas (sensitivity of 90%) and for detecting low-grade pulmonary NETs.
- Using computational tools, ^{68}Ga-DOTATATE PET/CT can be used as an accurate tool for assessing disease burden.

^{68}Ga-DOTATATE PET/CT for tailoring NET management

- ^{68}Ga-DOTATATE PET/CT imaging impacts the management of patients with NETs by identifying lesions that are candidates for resection or by identifying multiple unresectable lesions that should be treated with systemic therapy.
- SSTR-based PET/CT has been shown to be useful in the management of NETs in patients with hereditary syndromes (multiple endocrine neoplasia syndrome type 1, von Hippel-Lindau disease).

^{68}Ga-DOTATATE PET/CT utility for follow-up & prognosis prediction

- Demonstrating the avidity of the tumor to SSTR-based tracers is required to determine the eligibility of a patient for peptide-receptor radionuclide therapy (PRRT).
- Several baseline ^{68}Ga-DOTATATE PET/CT imaging parameters may be associated with PRRT success including maximum standardized uptake value (SUVmax), tumor-to-liver SUVmax ratio and tumor-to-spleen SUVmax ratio.
- Textural tumor features, a surrogate for intratumoral SSTR heterogeneity, were found to predict survival in patients with NETs.
- A decrease in ^{68}Ga-DOTATATE uptake following PRRT has been associated with a lower risk of disease progression and a clinical response to treatment.
- Low ^{68}Ga-DOTATATE PET/CT-derived SUVmax was associated with a poor prognosis in patients with NETs.

Dual-tracer PET/CT

- Dual-tracer PET/CT refers to imaging with two different tracers, one using ^{18}F-FDG for measuring the tumor metabolic rate and the other for demonstrating the expression of SSTRs.
- In patients with high-grade NETs, tumor assessment was found to be more comprehensive when dual-tracer PET/CT was integrated, and the use of ^{18}F-FDG PET/CT slightly improved the accuracy of ^{68}Ga-DOTATATE PET/CT alone in patients with pancreatic NETs.
- Dual-tracer PET/CT has been shown to be helpful in characterizing pulmonary NETs, with atypical and high-grade pulmonary NETs showing less ^{68}Ga-DOTATATE and more ^{18}F-FDG avidity and with an inverse pattern among typical tumors.
- Based on dual-tracer PET/CT, high-risk lesions with higher ^{18}F-fluorodeoxyglucose and lower ^{68}Ga-DOTATATE avidity can be selected for biopsy with potentially better diagnostic accuracy.

Financial & competing interests disclosure

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