Neuroendocrine Tumor Diagnosis and Management: $^{68}$Ga-DOTATATE PET/CT

OBJECTIVE. The purpose of this article is to provide a review of the use of $^{68}$Ga-tetraazacyclododecane-tetraacetic acid–DPhe1-Tyr3-octreotate (DOTATATE) PET/CT, a functional imaging modality for assessment of well-differentiated neuroendocrine tumors (NETs). It has become the preferred imaging modality for initial diagnosis, selection of patients for peptide receptor radionuclide therapy, and localization of unknown primary tumors. The National Comprehensive Cancer Network guideline has added $^{68}$Ga-DOTATATE PET/CT as an appropriate test in the management of NETs.

CONCLUSION. In combination with FDG PET/CT, $^{68}$Ga-DOTATATE PET/CT can noninvasively assess tumor heterogeneity, especially in G2 and G3 NETs, for personalized management of patients.

Neuroendocrine tumors (NETs) are a rare, heterogeneous group of tumors, most commonly arising in the gastroenteropancreatic (GEP) tract and lungs [1]. These tumors show overexpression of somatostatin receptors (SSTRs) on their cell membrane, more frequently type 2 [1]. In recent years, the incidence and prevalence of NETs have increased, partly because of early detection and longer survival from improved therapy. In a retrospective population-based study, Dasari et al. [2] found a 6.4-fold increase in age-adjusted incidence from 1973 to 2012 (6.98 per 100,000 patients).

SSTR-based $^{68}$Ga-tetraazacyclododecane-tetraacetic acid (DOTA)–peptide PET/CT is an exciting imaging modality that has shown significant advantages over conventional imaging in diagnosis and management of NETs [3]. According to the Society of Nuclear Medicine and Molecular Imaging (SNMMI) appropriateness use criteria [3], SSTR PET should replace $^{111}$In-pentetreotide scintigraphy in all instances in which SSTR scintigraphy is being used. In the recently updated National Comprehensive Cancer Network (NCCN) guidelines, $^{68}$Ga-DOTA-DPhe1-Tyr3-octreotate (DOTATATE) PET/CT has been added as an appropriate evaluation tool along with site-specific anatomic imaging using multiphase CT, multiphase MRI, or endoscopic ultrasound [4]. According to the SNMMI appropriate use criteria guidelines, SSTR PET should be the preferred imaging modality for initial diagnosis, selection of patients for peptide receptor radionuclide therapy (PRRT), and localization of unknown primaries [3, 5].

2017 World Health Organization Classification of Neuroendocrine Tumors and Neuroendocrine Carcinoma

The World Health Organization (WHO) uses mitotic count and the level of the nuclear protein Ki-67, which is associated with cellular proliferation, to classify GEP neuroendocrine neoplasms (NENs) [6]. NENs of the lungs, also called pulmonary carcinoids, are classified according to their mitotic count rate and the presence of necrosis [7]. In 2010, the WHO updated its classification of GEP NENs. Pancreatic NENs are classified into three grading subgroups on the basis of mitotic activity and Ki-67 index. Regardless of size and anatomic extent of the tumor, G1 and G2 NENs with well-differentiated morphology were designated as NETs; G3 NENs were poorly differentiated neuroendocrine carcinomas (NECs) of small or large cell type [8].

Poorly differentiated GEP NENs have a poorer outcome than well-differentiated tumors. Poorly differentiated NEN responds to cisplatin in more than 50% of cases versus less than 15% of well-differentiated tumors.
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**TABLE 1: World Health Organization Classification 2017**

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<th>Characteristic</th>
<th>Well-Differentiated Neuroendocrine Tumor</th>
<th>Poorly Differentiated Neuroendocrine Carcinoma</th>
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<tr>
<td>Grade</td>
<td>G1</td>
<td>G2</td>
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<td>Ki-67 index (%)</td>
<td>≤ 3</td>
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[9]. The NORDIC NEC study [10] found that G3 NECs with a Ki-67 index less than 55% do not respond well to platinum-based chemotherapy, in contrast to G3 NECs with a Ki-67 index greater than 55%. In light of these observations, the new classification was appropriate, because tumors at the lower end of the G3 range are in fact well-differentiated NETs with an elevated proliferation rate. In addition, Basturk et al. [11] found that a morphologically well-differentiated pancreatic NET that would be classified as G2 on the basis of mitotic rate and G3 on the basis of Ki-67 index had a significantly better clinical outcome than a morphologically poorly differentiated NEC. On this evidence, the WHO classification for pancreatic NE killer was updated in 2017 (Table 1). The new classification divided G3 tumors into two subgroups: well-differentiated NETs (Ki-67 = 20–50%) and poorly differentiated NECs (Ki-67 > 50%).

**Somatostatin Receptor Imaging**

The first SSTR imaging was performed in 1989 with a gamma camera using 123I-Tyr3-octreotide for carcinoids and endocrine pancreatic tumors [12, 13]. Indium-111 pentetreotide became the most widely used radiotracer with varying sensitivity (67–100%) using planar, SPECT, and SPECT/CT imaging 4 and 24 hours after injection [14]. In a prospective study, Deppen et al. [15] compared 68Ga-DOTATATE and 111In-pentetreotide imaging in patients with NETs and found 111In-pentetreotide SPECT/CT to be more sensitive than planar imaging only or planar imaging plus SPECT. In addition, the sensitivity of 68Ga-DOTATATE imaging (96% [95% CI, 86–100%]) was higher than that of 111In-pentetreotide imaging with all methods (72% [95% CI, 58–84%]). When compared with 111In-pentetreotide SPECT/CT, 68Ga-DOTATATE PET/CT had higher sensitivity (97% [95% CI, 82–100%] vs 65% [95% CI, 64–94%]). Deppen et al. found that the specificity was the same for 68Ga-DOTATATE PET/CT and 111In-pentetreotide among all 111In-pentetreotide scan types and for the SPECT/CT subgroup (93% [95% CI, 77–99%]). Compared with available 68Ga-DOTATOC peptide PET/CT, gamma camera imaging with 111In-pentetreotide has several limitations including lower image quality, physiologic uptake that may restrict detection of small abdominal lesions, prolonged imaging protocol (planar imaging is generally performed at 4 and 24 hours and SPECT 24 hours after injection), and relatively high radiation dose to patients [16, 17] (Figs. 1A and 1B).

Gallium-68 DOTATATE, a selective SSTR type 2 PET tracer, has an affinity for SSTR type 2 that is 100 times higher than that of 111In-pentetreotide [18]. Although 68Ga-DOTA-d-Phe1-Tyr3-octreotide (DOTATOC), 68Ga-DOTA-l-Nal3-octreotide (DOTANOC), and 68Ga-DOTATATE can bind to SSTR type 2, these radiotracers have different affinity profiles for other SSTR subtypes. For example, 68Ga-DOTANOC has good affinity for SSTR types 3 and 5, and 68Ga-DOTATOC binds to SSTR type 5 (although with lower affinity than 68Ga-DOTANOC) [19].

For patient preparation, no special dietary or activity restrictions are needed [15]. Some authors recommend discontinuing cold octreotide therapy to avoid possible SSTR blockade: 1 day is suggested for short-acting and 3–4 weeks for long-acting analogs [19]. However, this suggestion is controversial and not practiced in many centers [19]. PET/CT acquisition typically begins 60 minutes after IV administration of the radiotracer and proceeds from the skull base to the mid thighs.

**Gallium-68–DOTATATE Biodistribution**

The pituitary gland, spleen, liver, adrenal glands, and urinary tract show significant uptake in normal biodistribution of 68Ga-DOTATATE, whereas the thyroid gland, salivary glands, and parotid glands show faint to mild homogeneous uptake [20, 21]. Because lung tissue mainly expresses SSTR type 4, the lungs generally show low 68Ga-DOTATATE uptake, reflecting the low expression of SSTR type 2. Homogeneous uptake is observed in the spleen and in the liver. Because the spleen contains T lymphocytes, the splenunculi can have a very high uptake, similar to the uptake in spleen (in a nodule left after splenectomy), or lower uptake than spleen (in accessory spleen) [22, 23]. The pancreatic head and uncinate process contain cells expressing SSTR and can frequently show uptake on SSTR imaging, awareness of which is important to avoid misinterpretations [20, 24–26] (Fig. 2). SSTRs are expressed widely throughout the distal nephron and collecting tubules in the kidneys, and the vasa recta express SSTR type 2 in high density. Gallium-68 DOTATATE is primarily excreted through the kidneys because of its hydrophilic properties [27–29].

**Neuroendocrine Tumor Imaging**

**Anatomic Imaging Modalities**

Traditionally, CT and MRI are used for initial staging and evaluation of NETs because they provide excellent anatomic detail of the tumor and have been shown to have good diagnostic accuracy [30, 31]. Primary NETs and their metastases generally show enhancement after administration of IV contrast material. The mean sensitivity of a CT scan is 73% for detecting primary tumor and 80% and 75% for hepatic and extrahepatic metastases, respectively [31]. MRI is the best conventional modality for detection of hepatic metastases in NETs [32, 33]. The reported sensitivity for MRI is 95.2% [33]. However, diagnostic accuracy of anatomic imaging is limited by constraints such as size and morphology of a lesion (Figs. 1C–1D). It can therefore miss subtle (subcentimeter) primary or metastatic lesions. In a recent literature review comparing diagnostic performance of 68Ga-DOTA-peptide PET with CT and MRI, SSTR PET (DOTATOC and DOTATATE) showed better performance than CT for detecting primary and metastatic disease. Gallium-68-DOTATOC PET also showed better performance (higher sensitivity and similar specificity) than MRI for detecting primary tumors [3].

**Gallium-68–DOTATATE PET/CT of Gastroenteropancreatic Neuroendocrine Tumors**

**Diagnosis and initial staging**—Diagnosis of suspected NETs is usually based on clinical suspicion, biomarkers (such as chromogranin A, synaptophysin, and neuron-specific enolase), and imaging and histopathologic findings, which also provide tumor proliferation rate (Ki-67 index). Recent imaging guidelines have suggested that SSTR PET should be the preferred imaging modality for initial diagnosis [3]. Several studies have shown the high diagnostic accuracy of 68Ga-DOTATATE PET/CT in diagnosis of primary NETs compared with conventional imaging modalities. According to one meta-
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Analysis including 22 studies and 2015 patients, 68Ga-DOTATOC, 68Ga-DOTANOC, and 68Ga-DOTATATE PET/CT had sensitivity of 93% and specificity of 91% for detection of primary tumor [34]. Accurate staging of NET is essential for optimizing patient management. In NET management, surgery is the only possible curative approach, but presence of metastases can preclude surgical resection. Metastases are common, and both indolent and aggressive NETs can metastasize [35, 36]. Therefore, 68Ga-DOTATATE PET/CT can help determine which patients will benefit from surgical resection.

For N staging, lymph node short-axis diameter of 10 mm on CT and MRI is generally used to differentiate benign from malignant lymph nodes [37]. However, benign reactive lymph nodes meeting this criterion (false-positive) or smaller lymph nodes with micrometastases (false-negative) can lead to misinterpretation. Additional functional information from 68Ga-DOTATATE PET/CT may help in assessing small lymph nodes. However, reactive lymph nodes can result in false-positives [38]. According to one study, 68Ga-DOTATOC PET/CT showed higher sensitivity than whole-body MRI for metastatic lymph nodes (100% vs 73%) [39]. Mesenteric lymph nodes are the second most common metastatic site of small bowel NET, with the liver being first. Accurate assessment of lymph node involvement is important for therapeutic decision making. For instance, conventional surgical techniques cannot be used in patients with involvement of lymph nodes at the level of the mesenteric root [40]. Albusus et al. [41] compared a combination of 68Ga-DOTATATE PET and contrast-enhanced CT with standalone contrast-enhanced CT in 54 patients with NETs and found that, on a per-patient basis, contrast-enhanced PET/CT achieved a higher sensitivity (92% vs 64%) and specificity (83% vs 59%) for lymph nodes.

For M staging, detection of distant metastases is a crucial step in deciding optimal management. Distant metastases can thwart curative surgical resection. Common sites of metastatic spread in GEP NETs are liver, peritoneum, lung, and bone [42, 43]. Gallium-68 DOTATATE PET/CT has good diagnostic accuracy to detect distant metastases and can have significant impact on patient management (Fig. 3). The liver is the most common site of metastases from GEP NETs, and MRI has been shown to have similar diagnostic performance to 68Ga-somatostatin-analog (SSA) PET [3]. Frilling et al. [44] examined 52 patients with NET and found that 68Ga-SSA PET identified additional liver metastases, extrapancreatic disease, or both that were undetected by CT or MRI in 22 of the 33 patients with liver metastases. Additionally, it altered management strategies in 60% of all patients, including cancellation of planned liver resection in 13 because of identification of unresectable extrapancreatic disease and modification of initially planned surgical approach in seven.

**Detection of recurrent disease—Recurrence of NETs after surgical resection is common. In a cohort of patients with pancreatic NETs, 42% developed recurrent disease after curative resection of the primary tumor, whereas 59% of a cohort of patients with small-bowel NETs developed recurrent disease [45]. Therefore, early detection of recurrence is important for therapeutic decision making. No imaging consensus guidelines for postsurgical follow-up are currently available. The 2017 NCCN guidelines suggest using multiphasic abdominopelvic CT or MRI, chest CT, SSTR imaging (SSTR scintigraphy or 68Ga-DOTATATE PET/CT), and biochemical evaluation as clinically indicated [46]. Tumor biomarkers can be helpful predictors of recurrence. However, tumor markers have certain limitations, specifically in patients with nonsecreting tumors or in identifying location of recurrence. For example, the plasma level of chromogranin A, the most commonly used tumor marker, can depend on the anatomic sites of primary tumor or metastases and does not reveal where recurrence is when levels are elevated [47].**

**Gallium-68 DOTATATE PET/CT is accurate in detection of recurrent NET. However, postsurgical inflammatory changes can take up DOTATATE, mimicking malignant activity. Therefore, clinical correlation including tumor biomarkers can be helpful. Haug et al. [45] evaluated diagnostic performance of 68Ga-DOTATATE PET/CT in detection of recurrent NETs. Sixty-three patients who had undergone primary curative resection of NETs were examined because of increased plasma levels of tumor markers (n = 27), because of clinical suspicion of recurrence (n = 6), or as part of regular follow-up examinations (n = 30). Final diagnosis of NET recurrence was determined in 29 patients. The presence or absence of recurrent disease was confirmed in 25 patients with histopathologic findings and in 38 patients with follow-up examinations during a median of 24 ± 14 months (mean, 25 months) after PET/CT. The authors found 94% sensitivity, 89% specificity, 85% positive predictive value, 96% negative predictive value, and 91% accuracy of 68Ga-DOTATATE PET/CT for detection of recurrent GEP NETs in 29 patients.**

**Identifying unknown primary site**—In 10–22% of all NETs, the primary tumor site is unknown [48–51]. Detection of the primary site is important because this knowledge can allow excision or tumor debulking, leading to symptom improvement. Initial suspicion is based on biochemical workup and clinical symptoms. The most common primary sites are the small intestine and the pancreas [51]. Gastrinomas are often located in the duodenum or stomach, whereas adrenocorticotropic hormone-secreting carcinoids are often located in the lung. The diagnostic approach is usually based on suspected site. For example, if the primary site is suspected to be in the gastrointestinal tract, the diagnostic approach could include upper and lower endoscopy and CT enterography. Whole-body PET/CT, with SSTR-targeted imaging, has advantages in these cases (Fig. 4). In a series of 59 patients with biopsy-proved NET but an unknown primary tumor site, after evaluation with ultrasound, CT, MRI, and selective use of endoscopic ultrasound, a primary tumor was localized with 68Ga-DOTANOC in 59% of cases and with CT in 20% [52]. Using 68Ga-DOTATOC, Schreiter et al. [53] and Menda et al. [54] were able to determine a primary tumor site in 46% (111In-octreotide showed a detection rate of only 8%) and 38% of the cases, respectively. The most common site of false-positive interpretation in the study by Menda et al. was in the pancreatic head, particularly the uncinate process, which may display focal or diffuse intense uptake related to the concentration of pancreatic polypeptide cells. Lymphoid hyperplasia containing activated lymphocytes and macrophages (in the ileum and gastric fundus) can have a similar appearance [19, 54].

**Therapeutic applications**—NETs vary in aggressiveness and are graded from G1 to G3 on the basis of level of differentiation, Ki-67 proliferation index, mitotic count, or some combination of those factors. This grading has important therapeutic implications because unresectable well-differentiated G1 and G2 tumors with high expression of SSTR can potentially be treated with targeted molecular therapy PRRT, which binds the SSTR receptors on NETs.
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[55, 56]. The same peptide (octreotate) and linker (DOTA) are labeled with radioactive isotope (e.g., \(^{177}\)Lu-DOTA-octreotate, \(^{90}\)Y-DOTA-octreotate) that emits radiation and causes DNA damage. For bulky tumors, \(^{90}\)Y is preferred because it releases more energy and has more tissue penetration; \(^{177}\)Lu is preferred for small tumors [57]. Because they have the same target site as an SSA (DOTATATE), therapy with these isotopes can only be used in patients with SSTR-positive disease. PRRT has shown promising results [58, 59]. Some studies have reported that preoperative PRRT for unresectable NENs was associated with tumor shrinkage that could eventually enable operative intervention [60]. Lutetium-177-DOTA-octreotate has very low occurrence of side effects and has been shown to improve survival rate and quality of life in patients with NETs [60].

Dual imaging with FDG PET/CT and SSTR PET can be of significant value because it allows whole-body tumor grading and assessment of tumor heterogeneity (including expression of SSTR) (Fig. 5). This ability stems from the fact that DOTATATE (SSTR-peptide) uptake is directly proportional to SSTR expression, which is directly related to tumor cell level of differentiation (i.e., poor differentiation [G3] means low DOTATATE binding). On the other hand, FDG uptake by tumor cells depends on metabolic activity; high-grade tumors are known to be more metabolically active. This phenomenon, known as the flip-flop phenomenon, can be used as a surrogate for whole-body (primary and metastatic sites) tumor histopathologic grading and characterization [61]. This method has a number of advantages over traditional histopathologic tumor grading, including whole-body tumor characterization, convenience, non-invasiveness, and avoidance of sampling errors. Chan et al. [62] proposed a dual-tracer NET PET score for characterizing lesions and as a prognostic tool. They graded lesions on a 5-point scale from P1 (purely SSTR-positive lesions without FDG uptake above background) to P5 (significant FDG-positive and SSTR-negative disease). In the intermediate categories of P2 to P4, lesions exhibit positivity on both scans with progressive increase in FDG uptake (relative to uptake on SSTR PET) moving from P2 to P4. P0 indicates a normal scan on both FDG and SSTR PET. They found overall survival to be significantly associated with the NET PET grade. Combined \(^{68}\)Ga-DOTATATE and FDG PET/CT was found to be helpful in the individual therapeutic approach of GEP NETs [63]. Panagiotidis et al. [64] showed FDG PET/CT plays a significant clinical role in combination with \(^{68}\)Ga-DOTATATE in poorly differentiated NETs. Lesions expressing \(^{68}\)Ga-DOTATATE would respond to therapy with \(^{177}\)Lu-DOTATATE; lesions that are FDG-avid but do not show \(^{68}\)Ga-DOTATATE uptake are more likely to respond to chemotherapy or need another mode of treatment. This approach will facilitate more precise therapy decision making for individual patients.

**Pheochromocytoma and paraganglioma**—No biomarkers have been found that can differentiate between benign and malignant pheochromocytomas (PCCs) and paragangliomas (PGLs), but functional imaging can play a pivotal role [11]. FDG PET is commonly used for this purpose. However, in direct comparison, a similar number of lesions was detected with \(^{68}\)Ga-DOTATATE PET/CT (96.2% vs 91.4%), but significantly greater lesion-to-background contrast was seen compared with FDG PET/CT. Similar to other NETs, complementary information from FDG and DOTATATE imaging can be helpful for tumor characterization and therapeutic decision making [67]. Chang et al. [67] suggested that given the high specificity, patient convenience, and lack of confounding brown fat activation, \(^{68}\)Ga-DOTATATE PET/CT should be considered the ideal first-line investigation for imaging PGLs and PCCs (Figs. 6 and 7). Gene mutations, especially succinate dehydrogenase subunit B (SDHB), were found to be associated with metastatic PCCs and PGLs in more than 40% of patients [68]. Janssen et al. [69] compared the detection rate of \(^{68}\)Ga-DOTATATE, \(^{18}F\)-fluorodopa, \(^{18}F\)-fluorodihydroxyphenylalanine (F-DOPA), and FDG as well as CT and MRI in 17 patients with SDHB-related metastatic PCCs and PGLs. The authors found that \(^{68}\)Ga-DOTATATE PET/CT has the highest lesion-based detection rate with 98.6% and FDG has the second highest detection rate with 85.8%. F-DOPA had a low lesion-based detection rate of 51.9%, which the authors interpreted might be explained by tumor dedifferentiation associated with loss of the noradrenergic transporter in these patients. In another study by Jha et al. [70], diagnostic performance of \(^{68}\)Ga-DOTATATE and FDG PET/CT was evaluated in pediatric patients with SDHB-related PGLs and PCCs. The authors found that \(^{68}\)Ga-DOTATATE PET/CT has superiority in localization of lesions compared with FDG PET/CT, CT, and MRI [70].

**Neuroblastoma**—Neuroblastoma is the most common extracranial malignant solid tumor in childhood. Sixty-five percent of primary tumors are found in the adrenals and the remainder elsewhere along the sympathetic nervous chain [71]. They express SSTR (specifically SSTR type 2) in up to 77–89% of neuroblastomas [67]. Use of functional imaging can provide important information on disease extent as well as the presence of metastatic disease and suitability for PRRT therapy. Gallium-68 DOTATATE PET/CT has been shown to have greater sensitivity and specificity than \(^{131}\)I-metaiodobenzylguanidine SPECT/CT [7, 72].

**Pulmonary carcinoid**—Pulmonary carcinoids (PCs) account for 1–2% of all pulmonary malignancies [73]. PCs are divided into two categories according to the number of mitoses and the extent of necrosis: typical carcinoids (TCs) and atypical carcinoids [73]. TCs usually are more indolent and have better prognosis but show mild FDG uptake [74, 75]. Therefore, \(^{68}\)Ga-labeled SSAs have been proposed as a new tool in the diagnostic assessment of PCs (Fig. 8). In a study by Lococo et al. [75], \(^{68}\)Ga-DOTA-peptide PET/CT showed a better detection rate than FDG PET/CT (79% vs 55%).

**Medullary thyroid carcinoma**—Medullary thyroid carcinoma (MTC) is a NET of the parafollicular or C cells of the thyroid gland. MTC can be sporadic or, in a small number of cases, hereditary (multiple endocrine neoplasia type 2B). SSTR types 2 and 5 are the most frequent receptor expressions in MTC [76]. CT and MRI have an important role in preoperative evaluation for metastases, and up to 13% of cases can show distant metastases at presentation (and are usually associated with elevated calcitonin levels). Functional imaging including FDG PET/CT and \(^{68}\)Ga-DOTA are not routinely recommended for preoperative imaging [77, 78]. However, up to 50% of patients can develop recurrence or have residual disease after aggressive treatment. Gallium-68 DOTA-peptide PET/CT and FDG...
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PET/CT have complementary roles in postoperative assessment (Fig. 9). Gallium-68 DOTATATE PET/CT has been shown to be superior to 111In-octreotide SPECT/CT for the detection of recurrent MTC and distant metastases [79]. In one study, Treglia et al. [80] compared F-DOPA, FDG, and 68Ga-DOTATATE in 18 patients with residual or recurrent MTC suspected on the basis of elevated serum calcitonin levels and found F-DOPA to be the most sensitive and FDG PET to be the least sensitive of the three (72% vs 33% vs 17% for F-DOPA, 68Ga-DOTATATE, and FDG, respectively).

### Other Malignant and Benign Tumors

A wide variety of both benign and malignant neoplasms including breast cancer, colorectal cancer, gastric carcinoma, melanoma, lymphoma, hepatocellular carcinoma, renal cell carcinoma, sarcoma, small cell lung cancer, non–small cell lung cancer, or glioblastoma multiforme are known to express SSTR [81]. Therefore, 68Ga-DOTATATE PET/CT can be used for imaging and in management of these neoplasms (Fig. 10). Its potential use and value have yet to be fully characterized for patients with these tumors.

### Conclusion

Gallium-68 DOTATATE PET/CT is an advanced functional imaging modality for assessment of well-differentiated NETs. It should be the preferred imaging modality for initial diagnosis, selection of patients for PRRT, and localization of unknown primary tumors. The NCCN guideline has added 68Ga-DOTATATE PET/CT as an appropriate test in the management of NETs. In combination with FDG PET/CT, 68Ga-DOTATATE PET/CT can noninvasively assess tumor heterogeneity especially in G2 and G3 NETs for personalized management of patients.

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Fig. 1—Advantages of 68Ga-DOTATATE PET/CT over conventional imaging.
A, 64-year-old woman who underwent 68Ga-DOTATATE PET/CT and octreotide scanning for evaluation of metastases. Indium-111 octreotide SPECT/CT showed multiple focal liver lesions (white arrows) and primary ileal lesion (black arrow) on anterior planar image obtained 24 h after radiotracer administration.
B, Same patient as in A. After ileal primary tumor resection (6-week follow-up), multiple liver lesions were seen with better delineation on 68Ga-DOTATATE PET/CT (arrows) maximum-intensity-projection image.
C and D, 71-year-old man who underwent 68Ga-DOTATATE PET/CT for staging neuroendocrine tumor (NET) (after resection of rectal NET). Axial 68Ga-DOTATATE PET/CT fused images at aortic bifurcation level (C) and perirectal area (D) show 11-mm node at root of inferior mesenteric vessels (arrow, C) and 5-mm left perirectal node (arrow, D) with intense activity. These lesions were missed on original reading of axial contrast-enhanced CT images and only became apparent with knowledge of PET/CT findings.
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Fig. 2—Physiologic activity on $^{68}$Ga-DOTATATE PET/CT. Physiologic uptake can be seen in pituitary, salivary, thyroid, and adrenal glands as well as liver, spleen, and kidneys. Injection site in left arm is also seen.

Fig. 3—53-year-old man who underwent $^{68}$Ga-DOTATATE PET/CT for diagnosis and staging of suspected neuroendocrine tumor (NET) after 9-mm hyperenhancing lesion was seen in distal ileum on MRI enterography. A–C, Maximum-intensity-projection CT image (A) and axial PET/CT fused images (B and C) show small avid lesion in distal ileum (white and black arrows, A and B) and lesions in liver (red arrows, A and C). Biopsy confirmed well-differentiated NET.
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Fig. 4—53-year-old man who underwent surgical resection of incidental mesenteric mass that was found to be well-differentiated neuroendocrine tumor (NET) on histopathology. Subsequent 68Ga-DOTATATE PET/CT was performed to find primary NET site. A and B, Coronal maximum-intensity-projection CT image (A) and axial PET/CT fused image (B) show small avid lesion in distal small bowel (arrow) with no evidence of metastatic disease. Surgery confirmed primary NET.

Fig. 5—Complementary roles of 68Ga-DOTATATE PET/CT and FDG PET/CT. A and B, 45-year-old woman with biopsy-proven well-differentiated G2 neuroendocrine tumor (NET) with Ki-67 index of 5%. Coronal maximum-intensity-projection FDG PET/CT image (A) shows no abnormality, but coronal maximum-intensity-projection 68Ga-DOTATATE PET/CT image (B) obtained 2 months later shows multiple bone metastases and primary ileal lesion. C and D, 75-year-old man with biopsy-proven well-differentiated G3 NET with Ki-67 index of 25%. Coronal maximum-intensity-projection FDG PET/CT image (C) shows large right posterior mediastinal nodal mass (arrow, C). 68Ga-DOTATATE PET/CT (D) performed 4 days later shows only faint activity (arrow, D) in mass.
Fig. 6—20-year-old woman who underwent MRI (not shown), which revealed incidental left retroperitoneal mass most consistent with paraganglioma (nongastroenteropancreatic neuroendocrine tumor). A and B, Anterior maximum-intensity-projection ⁶⁸Ga-DOTATATE PET/CT image (A) and axial PET/CT fused image (B) obtained for confirmation and staging of paraganglioma show large, avid left retroperitoneal mass near organ of Zuckerkandl (arrow) with no evidence of metastatic disease.

Fig. 7—46-year-old man with malignant pheochromocytoma in right adrenal gland. Axial fused PET/CT image shows necrotic center in lesion with peripheral ⁶⁸Ga-DOTATATE uptake.

Fig. 8—70-year-old woman with pulmonary carcinoids whose case illustrates complementary roles of FDG and ⁶⁸Ga-DOTATATE PET/CT. A, FDG PET/CT scan obtained in 2009 to evaluate known lung lesion present since 1997 that shows mild FDG uptake (arrow). Patient underwent ⁶⁸Ga-DOTATATE study after biopsy showed lesion was typical carcinoid tumor. B, Gallium-⁶⁸ DOTATATE image shows highly avid lesion in left upper lobe with stable size (arrow) since 2009. Mild FDG uptake and intense ⁶⁸Ga-DOTATATE images are consistent with typical carcinoid tumor.
A 56-year-old man with medullary thyroid carcinoma in whom 68Ga-DOTATATE PET/CT was performed for restaging due to elevated serum calcitonin (>2000 pg/mL) and carcinoembryonic antigen (>500 ng/mL) levels.

A and B, Maximum-intensity-projection CT image (A) and sagittal PET/CT fused image (B) show multiple bone metastases (arrows) located in bilateral proximal humeri, bilateral ribs, multiple vertebral bodies, pelvic bones, and bilateral femurs with high somatostatin receptor expression.

Fig. 10—Other malignant and benign tumors. A, 46-year-old woman with glomus tumor with succinate dehydrogenase subunit B mutation. Patient underwent CT and MRI evaluation for paragangliomas. Both studies (not shown) showed left jugular foramen paraganglioma. Patient underwent 68Ga-DOTATATE imaging for subsequent antitumor treatment strategy and restaging. Axial fused PET/CT image shows highly 68Ga-DOTATATE–avid lesion (arrow) in left jugular fossa.

B, 39-year-old man with von Hippel–Lindau syndrome causing posterior fossa hemangioblastomas as well as bilateral pheochromocytomas, left paraganglioma, and left renal cell carcinoma. He had undergone bilateral adrenalectomy, paraaortic paraganglioma resection, and left nephrectomy. Gallium-68 DOTATATE PET/CT was performed for evaluation of persistent posterior fossa lesions with elevated metanephrine levels and restaging. Axial fused PET/CT image shows intensely 68Ga-DOTATATE–avid posterior fossa hemangioblastoma (arrow).

C, 48-year-old woman with medullary thyroid carcinoma who underwent 68Ga-DOTATATE PET/CT for peptide receptor radionuclide therapy planning. Axial fused PET/CT image shows high somatostatin receptor expression in fibroadenoma (arrow) that had previously been detected in left breast.