

# Somatostatin Receptor Imaging with $^{68}\text{Ga}$ DOTATATE PET/CT: Clinical Utility, Normal Patterns, Pearls, and Pitfalls in Interpretation<sup>1</sup>

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**Abbreviations:** DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DTPA = diethylenetriaminepentaacetic acid, EANM = European Association of Nuclear Medicine, ENETS = European Neuroendocrine Tumor Society, FDA = U.S. Food and Drug Administration, FDG = 2-[fluorine-18]fluoro-2-deoxy-D-glucose, MIBG = metaiodobenzylguanidine, MIP = maximum intensity projection, NET = neuroendocrine tumor, PRRT = peptide receptor radionuclide therapy, SSTR = somatostatin receptor, SUV = standardized uptake value, TIO = tumor-induced osteomalacia

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See discussions on this article by Del Rivero and Libutti (pp 516–518) and Delbeke (pp 518–519).

Gallium 68 ( $^{68}\text{Ga}$ ) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate (DOTATATE, GaTate) positron emission tomography (PET)/computed tomography (CT) is an imaging technique for detecting and characterizing neuroendocrine tumors (NETs). GaTate, a somatostatin analog, has recently been accorded orphan drug status by the U.S. Food and Drug Administration, thereby increasing interest in and availability of this radiotracer. GaTate PET/CT allows whole-body imaging of cell surface expression of somatostatin receptors (SSTRs) and is rapidly evolving as the new imaging standard of reference for the detection and characterization of NETs. The authors discuss the normal appearance at GaTate PET/CT and the utility of this modality in a variety of these tumors, including gastrointestinal, pancreatic, and bronchial NETs as well as pheochromocytoma, paraganglioma, meningioma, and oncogenic osteomalacia. In addition, they discuss potential causes of false-positive findings, including pancreatic uncinate process activity, inflammation, osteoblastic activity, and splenosis. They also highlight the complementary role of 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) PET/CT, including the advantages of using both GaTate PET/CT and FDG PET/CT to evaluate sites of well- and poorly differentiated disease. The use of GaTate PET/CT together with FDG PET/CT allows identification of tumor heterogeneity, which provides prognostic information and can be pivotal in guiding biopsy. It also allows optimal patient management, including theranostic application of peptide receptor radionuclide therapy, and the restaging of patients following therapy.

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## Introduction

Somatostatin receptors (SSTRs) are present on the cell surface of neuroendocrine cells, providing a unique and specific molecular target for imaging. Somatostatin is a peptide hormone that binds to this receptor, thereby regulating neurotransmission, hormone secretion, and cell proliferation. Somatostatin generally exerts an inhibitory effect such as suppressing the release of pancreatic hormones or reducing smooth muscle contractions. Octreotide is a synthetic somatostatin analog with a half-life of approximately 90 minutes, much longer than that of somatostatin (2–3 minutes). Octreotide was first radiolabeled in 1983, allowing SSTR imaging with a nuclear medicine gamma camera (1).

SSTR imaging has been performed for several decades as an octreotide scan (2). To perform this scan, less than 10  $\mu\text{g}$  of the peptide is radiolabeled with indium 111 ( $^{111}\text{In}$ ) and injected intravenously. Planar whole-body images are acquired, followed by single photon emission computed tomography (SPECT)/computed

## TEACHING POINTS

- Uptake at physiologic and pathologic sites may change in patients who undergo concomitant short- or long-acting somatostatin analog therapy, which competes with the radiotracer for bioavailability. We generally discontinue short-acting octreotide for 12–24 hours and perform imaging in the week before the next dose of long-acting octreotide, which is typically administered monthly.
- Given its high accuracy compared with conventional imaging techniques, GaTate PET/CT should be considered the first-line diagnostic imaging modality of choice for tumors with high SSTR expression, such as gastrointestinal and pancreatic NETs. In particular, GaTate PET/CT greatly impacts management by allowing identification of additional sites of disease when surgery with curative intent is being contemplated.
- GaTate PET/CT and FDG PET/CT are complementary and help identify both well- and poorly differentiated phenotypes, thereby allowing tumor characterization, prognostication, and better selection of appropriate therapy for individual patients.
- Causes of interpretative pitfalls include prominent pancreatic uncinuate process activity, inflammation, osteoblastic activity (degenerative bone disease, fracture, vertebral hemangioma), splenunculi or splenosis, and benign meningioma.
- SSTR PET/CT also plays a major role in a number of other tumors with high levels of SSTR expression, including pheochromocytoma, paraganglioma, neuroblastoma, meningioma, and mesenchymal tumors causing oncogenic osteomalacia.

tomography (CT) at 24 hours. Further imaging is sometimes performed at 48–72 hours to help differentiate pathologic from physiologic bowel uptake, although SPECT/CT usually obviates further delayed acquisitions.

SSTR positron emission tomography (PET)/CT is now possible by substituting gallium 68 (<sup>68</sup>Ga) for <sup>111</sup>In. PET/CT provides vastly superior detail and speed compared with conventional gamma camera imaging with <sup>111</sup>In (3). This procedure is combined with whole-body tomographic imaging and multisection CT, allowing detailed anatomic correlation. <sup>68</sup>Ga is a generator-produced positron emitter that allows on-site, on-demand availability; it should not be confused with <sup>67</sup>Ga, which is a single photon emitter. <sup>68</sup>Ga has a short half-life of 68 minutes, compared with 2.8 days for <sup>111</sup>In, resulting in a lower radiation dose to the patient, with an effective dose of 2.1 mSv for a 100-MBq administration (4,5). SSTR PET/CT is performed 45–60 minutes after radiotracer injection. The European Association of Nuclear Medicine (EANM) recently published procedural guidelines for nuclear medicine specialists in recommending, performing, reporting, and interpreting SSTR PET/CT studies (6).

<sup>68</sup>Ga is chelated (linked) to the peptide by means of the organic compound 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (Fig 1). In addition to the aforementioned benefits provided by PET, the use of the

DOTA chelator and a variety of newer-generation somatostatin analogs results in a higher-affinity radiopharmaceutical compared with conventional diethylenetriaminepentaacetic acid (DTPA)–octreotide imaging. These analogs are typically abbreviated as DOTATATE (GaTate), DOTATOC (GaToc), and DOTANOC (GaNoc) (Table 1). The clinical choice of a particular analog is often driven by local availability, with studies demonstrating only subtle differences in clinical utility (7). We have chosen to primarily use <sup>68</sup>Ga-DOTATATE (GaTate), since it has the highest affinity for SSTR subtype 2 (SSTR 2), which tends to be most overexpressed in neuroendocrine tumors (NETs) (8). It is also the peptide that is most commonly used for radionuclide therapy with lutetium 177 (<sup>177</sup>Lu) or yttrium 90 (<sup>90</sup>Y).

The availability of SSTR PET/CT has varied geographically owing to regulatory issues regarding the <sup>68</sup>Ga generator and radiotracer synthesis. However, availability has steadily increased, particularly in Europe, Asia, and Australia, since the first description of GaToc PET/CT in 2001 (9), with over 60 centers around the world performing SSTR PET/CT as of this writing. There are now several commercially available <sup>68</sup>Ga generators and automated synthesis units for radiotracer production. GaTate has recently been accorded orphan drug status by the U.S. Food and Drug Administration (FDA), thereby increasing interest in and availability of this emerging imaging technique.

In this article, we discuss SSTR PET/CT in terms of physiologic distribution and grading of pathologic uptake, imaging of gastroenteropancreatic NETs, potential pitfalls, and utility beyond gastrointestinal NETs.

### Physiologic Distribution and Grading of Pathologic Uptake

The highest-intensity physiologic uptake of GaTate is seen in the spleen, followed by the adrenal glands, kidneys, and pituitary gland (Fig 2) (10). Moderately intense uptake is also seen in the liver, salivary glands, and thyroid gland. This biodistribution reflects a combination of specific receptor binding and nonspecific tissue handling of the peptide. Uptake in the endocrine organs, salivary glands, and spleen is mediated by expression of SSTR, whereas uptake in the kidneys and liver is not. The peptide is small enough to be filtered through glomeruli but is also partially reabsorbed in the proximal convoluted tubule, resulting in high activity in the collecting system and bladder as well as retained activity in the renal parenchyma. Variable physiologic uptake in the small and large intestine and gastric activity are seen; the exact mechanism of this uptake is unclear but may reflect variable degrees of neuroendocrine cell

Table 1: Somatostatin Analogs Currently in Use for SSTR PET/CT

Compound	Abbreviation	Receptor Subtypes
$^{68}\text{Ga}$ -DOTA-Tyr <sup>3</sup> -octreotate	$^{68}\text{Ga}$ -DOTATATE (GaTate)	SSTR 2
$^{68}\text{Ga}$ -DOTA-NaI <sup>3</sup> -octreotide	$^{68}\text{Ga}$ -DOTANOC (GaNoc)	SSTR 3, SSTR 5
$^{68}\text{Ga}$ -DOTA-TyI <sup>3</sup> -octreotide	$^{68}\text{Ga}$ -DOTATOC (GaToc)	SSTR 5

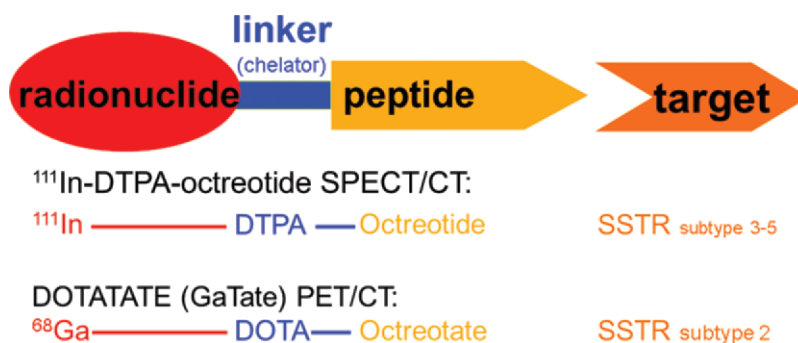
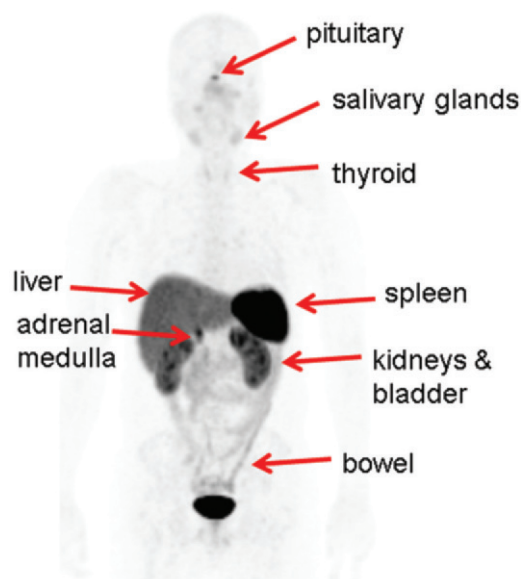


Figure 1. Chart illustrates how a radionuclide is linked to a peptide by means of a chelator for imaging of specific target agents.

Figure 2. Coronal maximum intensity projection (MIP)  $^{68}\text{Ga}$ -DOTATATE (GaTate) PET image shows the normal distribution of this radiotracer.

hyperplasia, since the appearance of the uptake is generally too rapid to reflect gastrointestinal excretion. Furthermore, unlike with octreotide imaging, gallbladder uptake is rarely seen. This is probably related to the earlier time point at which imaging occurs prior to hepatobiliary excretion.

Pathologic uptake can be graded with a semi-quantitative visual scoring system that consists of a scale from 0 to 4 and uses the liver and spleen as reference organs (Table 2) (11). This scoring system is named after Eric Krenning, who pioneered SSTR imaging at the Erasmus Medical Center in Rotterdam, the Netherlands. Although Krenning originally designed his scoring system for planar octreotide imaging, we have found it to be a valuable descriptor for reporting. Compared with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) PET/CT, there is minimal background activity in soft tissue and muscle, which contributes to high tumor-to-background contrast at pathologic sites. The combination of low background and high tumor uptake also contributes to a “sink effect,” whereby physiologic uptake, particularly in the spleen and liver, is reduced in patients with a high burden of disease (12). Uptake at physiologic and pathologic sites may change in patients who undergo concomitant short- or long-acting somatostatin analog therapy, which competes with the radiotracer for

bioavailability. We generally discontinue short-acting octreotide for 12–24 hours and perform imaging in the week before the next dose of long-acting octreotide, which is typically administered monthly.

### Imaging of Gastroenteropancreatic NETs

NETs arising from the gastrointestinal tract and pancreas are a heterogeneous disease with many different subtypes, ranging in aggressiveness from very indolent tumors that progress over decades to highly aggressive malignancies. Both indolent and highly aggressive tumors have the propensity to metastasize, and indolent tumors can cause

**Table 2: Krenning Scoring System for Visual Grading of Pathologic Uptake**

Score	Intensity
0	None (no uptake)
1	Very low
2	Less than or equal to that of liver
3	Greater than that of liver
4	Greater than that of spleen

Source.—Reference 11.

significant morbidity if they secrete bioactive hormones. These hormones can result in a variety of clinical syndromes, such as carcinoid syndrome and the hypoglycemic syndrome of insulinoma. The European Neuroendocrine Tumor Society (ENETS) and the World Health Organization have established grading systems that are based on immunohistochemical staining of Ki-67 protein, a marker of cellular proliferation. Currently, these grading systems stratify tumors into one of three grades: G1 NET (Ki-67  $\leq$  2%), G2 NET (Ki-67 = 3%–20%), and G3 neuroendocrine carcinoma (Ki-67 >20%). The latter group includes large- and small-cell variants, with small cell carcinoma representing the best-recognized variant.

### Accuracy of GaTate PET/CT Compared with Conventional Imaging

Multiple studies have shown GaTate PET/CT to be more accurate than conventional imaging, including octreotide SPECT/CT or contrast material-enhanced CT, in the diagnosis of gastrointestinal and pancreatic NETs. In a recent meta-analysis of 22 studies that included more than 2000 patients, GaTate PET/CT demonstrated a sensitivity of 93% and a specificity of 95% (13). In our experience, GaTate PET/CT represents the new standard of reference for imaging well-differentiated NETs. Consequently, GaTate PET/CT is subject to the “paradox of the gold standard,” in that there is no standard of reference by which to measure its accuracy. This is most evident when reviewing prior  $^{111}\text{In}$ -octreotide studies, which suggested a sensitivity of over 90% (14). However, in the GaTate PET/CT era, it is evident that the sensitivity of  $^{111}\text{In}$ -octreotide studies is substantially lower than these earlier studies suggest. Compared with other nuclear medicine studies, including FDG PET/CT, GaTate PET/CT has extraordinary target-to-background contrast, such that subcentimeter abnormalities that cannot be identified at conventional imaging can easily be identified (Fig 3). This high lesion contrast is reflected in high standardized uptake values (SUVs), which are significantly greater than

those seen with other PET radiotracers, including FDG. Given its high accuracy compared with conventional imaging techniques, GaTate PET/CT should be considered the first-line diagnostic imaging modality of choice for tumors with high SSTR expression, such as gastrointestinal and pancreatic NETs. In particular, GaTate PET/CT greatly impacts management by allowing identification of additional sites of disease when surgery with curative intent is being contemplated.

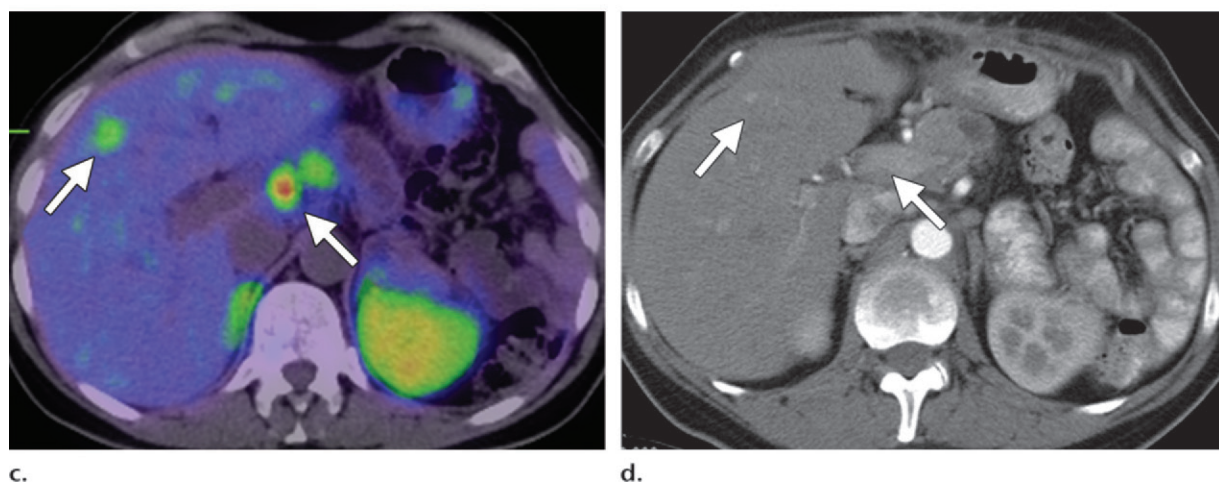
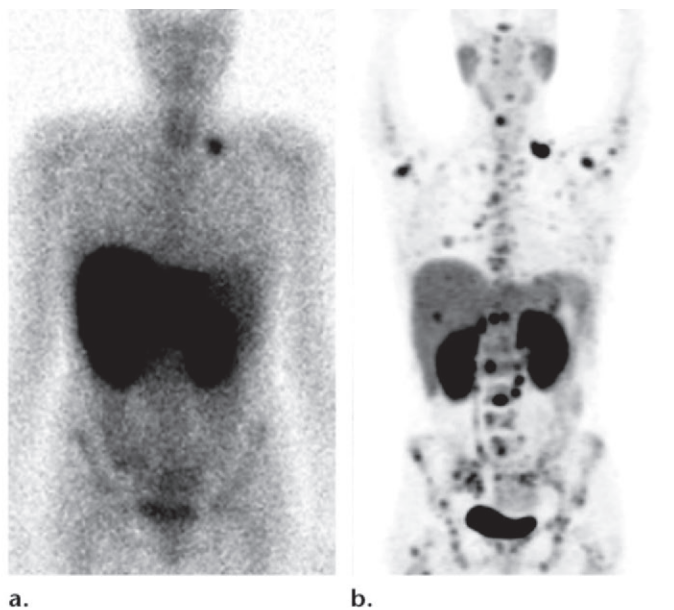
In addition to helping detect disease sites, molecular imaging offers the key advantage of being able to help characterize disease. When one is asked about the accuracy of GaTate PET/CT, it is important that the precise definition of “accuracy” be clear. Does the question refer to accuracy for the imaging of cell surface SSTR expression, or to accuracy for the detection of NETs? Studies demonstrate excellent correlation between SUV at GaTate PET/CT and SSTR 2 expression as determined by reverse polymerase chain reaction (15). Thus, GaTate PET/CT is an outstanding noninvasive technique for the imaging of cell surface SSTR expression and can be thought of as “imaging histopathology.” If the questioner is asking about accuracy for the detection of NETs, one needs to probe further and ask what type of NET and what degree of tumor differentiation the questioner has in mind, since SSTR expression can be variable and is decreased in more poorly differentiated subtypes.

Depending on the avidity of uptake on GaTate PET/CT images, contrast-enhanced magnetic resonance (MR) imaging can be more sensitive for the detection of subcentimeter hepatic metastases. MR imaging is particularly valuable in the assessment of patients with limited hepatic disease at GaTate PET/CT who are deemed to be potential surgical candidates.

### Localizing Unknown Primary Tumors

In patients with NET from an unknown primary tumor, GaTate PET/CT is an effective tool for localization of the primary tumor. Such patients include those with a suspected NET on the basis of biochemical workup and clinical symptoms, such as functional pancreatic islet cell tumors including insulinoma, glucagonoma, VIPoma, and gastrinoma. It has been reported that only around 50% of insulinomas express SSTR 2; in our experience, however, the majority of such lesions, particularly those demonstrating features of malignancy, are positive at GaTate PET/CT. Gastrinomas are often located in the duodenum or stomach. Adrenocorticotrophic hormone-secreting carcinoid tumors, often located in the lung, are another example of a functional tumor that can be difficult to localize without GaTate PET/CT. This can have a major impact on management by confirming the

**Figure 3.** Pancreatic NET in a middle-aged woman with normal findings at contrast-enhanced CT (which included three-phase CT of the liver). (a) Planar  $^{111}\text{In}$ -octreotide image demonstrates a solitary left supraclavicular nodal abnormality. SPECT/CT showed the same finding. (b) MIP GaTate PET/CT image obtained 4 days later demonstrates extensive metastatic disease. (c) Axial FDG PET/CT image clearly depicts a pancreatic primary tumor (right arrow) and hepatic metastases less than 5 mm in size (left arrow). (d) Arterial phase CT image shows the primary tumor (right arrow) and the metastases (left arrow), which were evident only in retrospect. Most other focal abnormalities seen at CT represent sclerotic lesions. PET/CT characterizes these abnormalities as metastases by virtue of their high SSTR expression, with prior negative histopathologic findings due to sampling error. Previous biopsy had revealed “normal” bone, with an incorrect diagnosis of benign osteopoikilosis subsequently being made.



diagnosis and directing patients to curative surgery (Figs 4, 5). GaTate PET/CT also has a high detection rate for NETs in patients with multiple endocrine neoplasia (16).

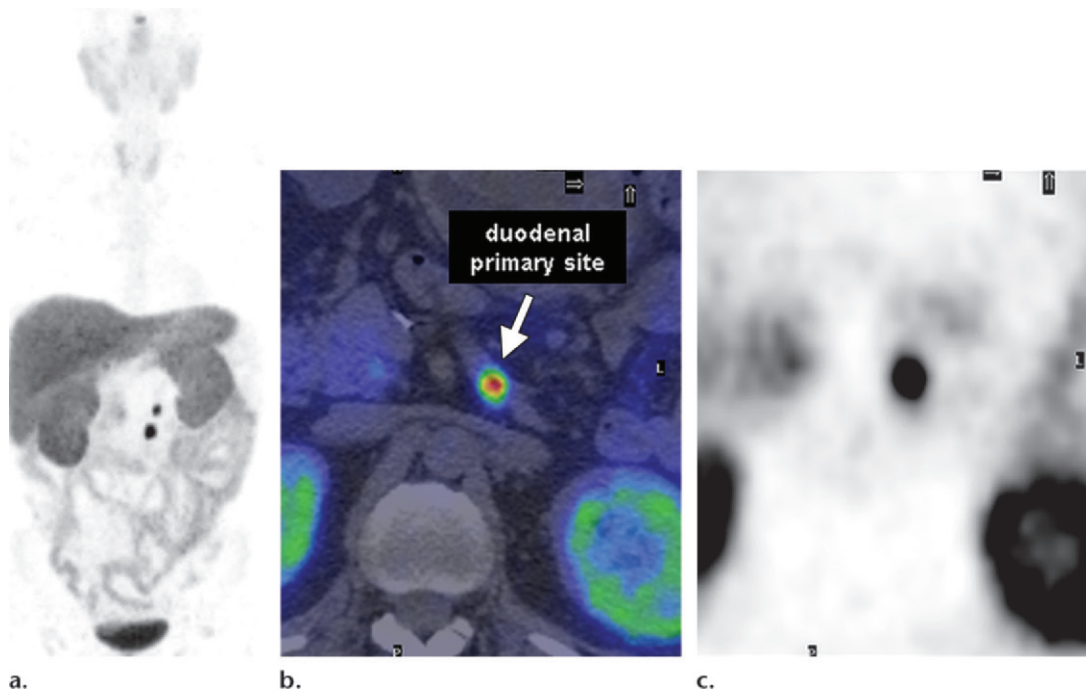
Patients with histologically proved NET at sites of distant metastases may also present with an unknown primary tumor site. Knowing the primary site of disease can assist in determining prognosis and choice of therapy. In patients with small bowel carcinoid tumor, excision of the primary tumor can still help improve symptoms, even in the presence of nonresectable distant metastases. In a series of 59 patients with biopsy-proved NET but an unknown primary tumor site after evaluation with multisec-tion CT, MR imaging, US, and selective use of endoscopic US, a primary tumor was localized with  $^{68}\text{Ga}$ -DOTANOC in 59% of cases (17).

### High Management Impact

Multiple studies have shown GaTate PET/CT to have a high impact on management (Table 3). In our own study of 59 consecutive patients, there was

an intermodality change in management in 47% of cases (24). High management impact included directing patients to curative surgery by identifying a primary tumor site and directing patients with multiple metastases to systemic therapy. GaTate PET/CT provided significant additional information compared with anatomic imaging and octreotide imaging in 69% and 83% of cases, respectively (24). This additional information most commonly consisted of identification of disease in bone, liver, pancreas, and nodal stations (in descending order of frequency). Importantly, management impact was similar in patients with negative or positive octreotide SPECT/CT findings, suggesting redundancy of this technique. Our recommended indications for the use of GaTate PET/CT in gastrointestinal and pancreatic NETs are listed in Table 4.

Given its high specificity, GaTate PET/CT can be used in selected patients to confirm the diagnosis of NET noninvasively. Incidental and asymptomatic sporadic NETs are increasingly being discovered, largely owing to the increased use



**Figure 4.** Gastrinoma in a 37-year-old man who presented with epigastric discomfort, vomiting, and weight loss. Gastroscopy demonstrated severe duodenal ulceration. The patient's gastrin level was markedly elevated, and his symptoms improved with a proton pump inhibitor, thereby confirming the diagnosis of a gastrinoma. MR imaging demonstrated a 1-cm nodule in the midpancreas. Octreotide SPECT demonstrated a congruent abnormality. Distal pancreatectomy and splenectomy were performed, but histologic analysis demonstrated a benign fatty lobule. (a) Postoperative GaTate PET image demonstrates two focal abnormalities. (b, c) Axial PET (b) and PET/CT (c) images allow confident localization of the primary tumor to the junction of the third and fourth parts of the duodenum (arrow in b). PET and PET/CT also demonstrated an adjacent subcentimeter nodal metastasis. This case highlights the nonspecificity of anatomic imaging, even when an abnormality is detected, and the exquisite accuracy of GaTate PET/CT in disease staging.

of cross-sectional imaging. A recent study showed that GaTate PET/CT can be used to confirm the diagnosis of NET, and that in selected patients with pancreatic NETs less than 2 cm in size, non-surgical management is safe (25).

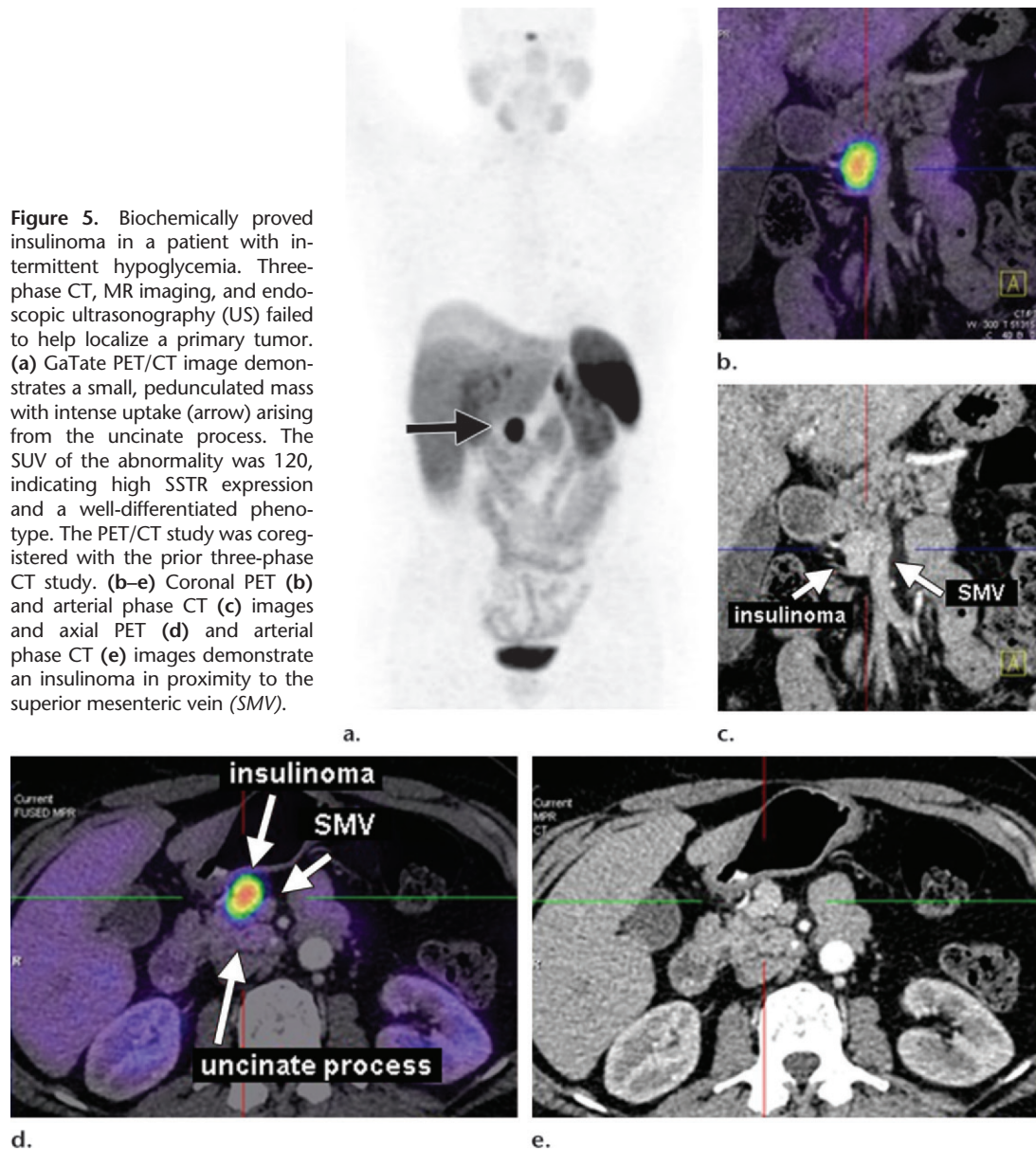
### Complementary Roles of GaTate PET/CT and FDG PET/CT for Tumor Grading and Characterization

G1 tumors are well differentiated and resemble the neuroendocrine cells from which they arise. As such, they typically retain high levels of SSTR expression like the cell surface of normal neuroendocrine cells, and sometimes they secrete a variety of hormones. More poorly differentiated tumors are less like normal neuroendocrine tissue, with consequent decreased SSTR expression, inability to produce hormones, and uncontrolled proliferation. Such tumors are typically considered to be G3 tumors in the ENETS grading system, and, congruent with the absence of SSTR expression, are not visualized at GaTate PET/CT. Conversely, such tumors usually have high glycolytic metabolism and therefore are well visualized at FDG PET/CT. Thus, there is a “flip-flop” phenomenon in which GaTate PET/CT and

FDG PET/CT findings are inversely related at either end of the ENETS spectrum. G2 tumors, representing the middle of the spectrum, can demonstrate uptake of both GaTate and FDG (Table 5). GaTate PET/CT and FDG PET/CT are complementary and help identify both well- and poorly differentiated phenotypes, thereby allowing tumor characterization, prognostication, and better selection of appropriate therapy for individual patients.

Tumor grade is traditionally based on the results of a single biopsy performed at the site that is most easily and safely accessible by means of percutaneous core biopsy or surgical excision. Molecular imaging, however, can allow whole-body tumor characterization, with sites of well- and poorly differentiated disease demonstrated at GaTate PET/CT and FDG PET/CT, respectively (26). The fact that different grades of disease are seen at different sites reflects tumor heterogeneity and highlights the limitations of a single random biopsy (Fig 6). Knowledge of this phenomenon is pivotal in guiding patient management. GaTate PET/CT can be used to identify patients who may benefit from octreotide hormonal therapy, which can be successful in controlling symptoms due to

**Figure 5.** Biochemically proved insulinoma in a patient with intermittent hypoglycemia. Three-phase CT, MR imaging, and endoscopic ultrasonography (US) failed to help localize a primary tumor. (a) GaTate PET/CT image demonstrates a small, pedunculated mass with intense uptake (arrow) arising from the uncinate process. The SUV of the abnormality was 120, indicating high SSTR expression and a well-differentiated phenotype. The PET/CT study was coregistered with the prior three-phase CT study. (b–e) Coronal PET (b) and arterial phase CT (c) images and axial PET (d) and arterial phase CT (e) images demonstrate an insulinoma in proximity to the superior mesenteric vein (SMV).



hormone secretion but also has antiproliferative effects. GaTate PET/CT can also help identify patients who are suitable for PRRT with  $^{177}\text{Lu}$ - or  $^{90}\text{Y}$ -DOTA-octreotate (Fig 7) (2).

FDG PET/CT helps identify patients with adverse prognostic features. In a prospective series of 98 patients, FDG positivity was associated with a higher risk of death, with a hazard ratio of 10.3 (27). At multivariate analysis, an  $\text{SUV}_{\text{max}}$  greater than 3 was the only predictor of progression-free survival, superior to Ki-67 staining or anatomic parameters such as the number of hepatic metastases. We perform FDG PET/CT selectively in patients with clinical risk factors. Our recommended indications for the selective use of FDG PET/CT are shown in Table 6. When assessing suitability for PRRT, we use FDG PET/CT in these contexts to ensure that there are no sites of spatially discor-

dant FDG-avid SSTR-negative disease that cannot be targeted with PRRT.

### Restaging

Change in size is only a surrogate for true response, since some lesions may increase in size as cystic or liquefactive necrosis occurs following effective therapy. Such anatomic changes are observed more frequently if imaging is performed within a few weeks or months of therapy and can misinform decision making, since effective therapy can be misrepresented as progression on the basis of RECIST (Response Evaluation Criteria in Solid Tumors) criteria (Fig 8). Measurement is also subject to significant intra- and interreporter variability, whereas differences in contrast enhancement due to technique or changes in physiology also make a contribution. Changes in physiology are

**Table 3: Impact of SSTR PET/CT on Management**

Authors/Year of Study*	No. of Patients	Radiotracer	Change in Management	
			Type of Change	Percentage of Cases
Ambrosini et al/2010 (18)	90	DOTANOC	Stage or therapy	50%
Srirajaskanthan et al/2010 (19)	41	DOTATATE	Intermodality	71%
Frilling et al/2010 (20)	52	DOTATOC	Treatment	60%
Ruf et al/2010 (21)	64	DOTATOC	Intermodality	38%
Naswa et al/2011 (22)	109	DOTANOC	Intermodality	19%
Hofman et al/2012 (23)	59	DOTATATE	Intermodality	47%

\*Numbers in parentheses are reference numbers.

**Table 4: Authors' Recommended Indications for the Use of GaTate PET/CT in Gastrointestinal and Pancreatic NETs**

- Exclude more advanced disease prior to surgical intervention
- Localize primary tumor in patients with biochemical suspicion of NET
- Identify primary tumor in patients with known metastatic NET
- Confirm diagnosis of NET in patients with anatomic lesions that are suspicious for NET
- Identify patients who are likely to benefit from octreotide hormonal therapy or PRRT with <sup>177</sup>Lu- or <sup>90</sup>Y-DOTATATE

Note.—PRRT = peptide receptor radionuclide therapy.

**Table 5: FDG PET/CT and SSTR PET/CT in the Spectrum of NET Grading**

	ENETS Grade				
	G1	G2		G3	
		Low	High	Low	High
Ki-67 (%)	≤2	3–20		>20	
SSTR PET/CT	++	++	+	+	–
FDG PET/CT	–	–	+	+	++

Note.—Plus (+) and minus (–) signs indicate intensity of uptake.

particularly relevant in patients with carcinoid syndrome, since progressive carcinoid heart disease with consequent tricuspid regurgitation can result in significant changes in the enhancement of hepatic metastases. The ability to measure change in function both visually and with SUVs at PET/CT allows earlier and more accurate response by measuring SSTR expression and glycolytic metabolism with use of GaTate and FDG, respectively.

**Potential Pitfalls**

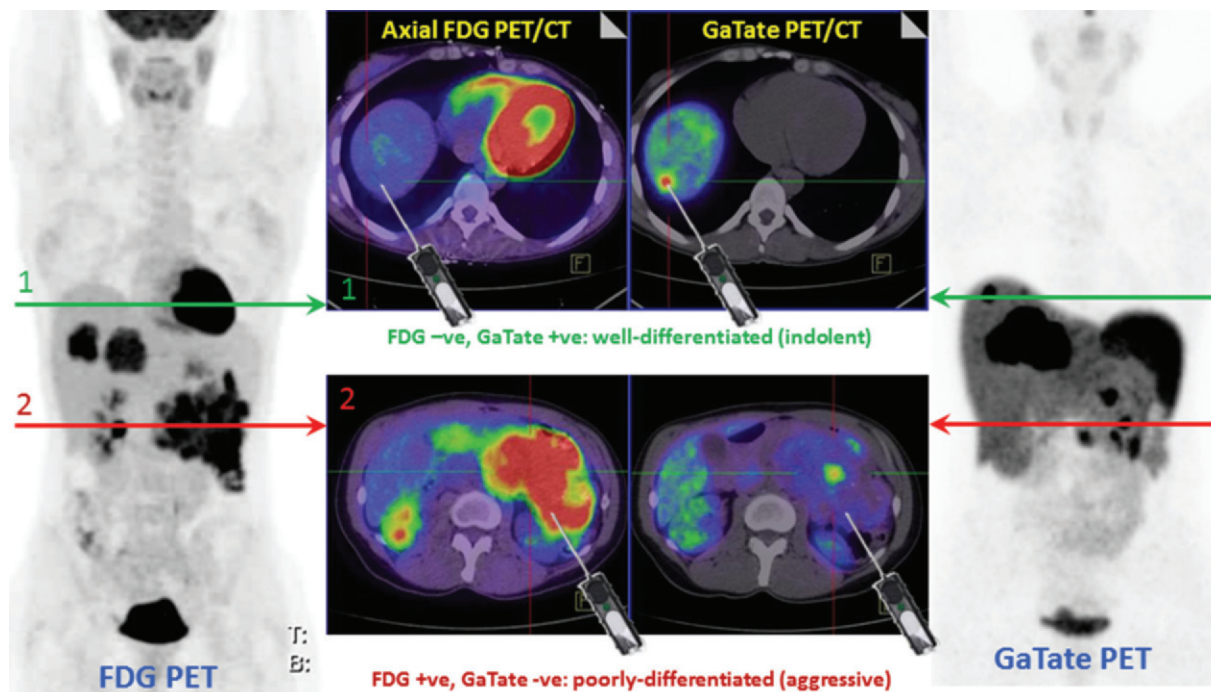
Although GaTate PET/CT is a highly sensitive and specific technique for NETs, the attending physician or radiologist must be aware of various physiologic and other pathologic processes in which cellular expression of SSTR can result in interpretative error (Table 7). Most of these processes

demonstrate low-intensity and/or nonfocal uptake, in contrast with the focal intense abnormality encountered in NETs. Causes of interpretative pitfalls include prominent pancreatic uncinate process activity, inflammation, osteoblastic activity (degenerative bone disease, fracture, vertebral hemangioma), splenunculi or splenosis, and benign meningioma.

**Physiologic Pitfalls**

**Pancreas.**—Prominent pancreatic uncinate process uptake is visualized in up to one-third of patients. Such a process can demonstrate intense uptake but usually has a curvilinear morphology or ill-defined edges that help distinguish it from the focal well-defined abnormalities seen in pathologic uptake. This appearance is often best appreciated





**Figure 6.** Tumor heterogeneity at combined FDG PET/CT–GaTate PET/CT. Metastatic insulinoma with a primary mass in the pancreatic tail filling the left upper quadrant and multiple hepatic metastases were evident at CT and MR imaging. Axial FDG PET/CT and GaTate PET/CT images through the liver (1, green arrows [top color panel]) demonstrate a metastasis that is GaTate positive but FDG negative, findings that are indicative of a well-differentiated lesion with high somatostatin cell surface expression. Axial FDG PET/CT and GaTate PET/CT images through the left upper quadrant (2, red arrows [bottom color panel]) demonstrate a largely GaTate-negative but FDG-positive lesion, findings that are indicative of a more poorly differentiated (aggressive) phenotype. In the absence of these results, core biopsy performed on the basis of CT or MR imaging findings could reveal either subtype, which might misinform decision making. (Reprinted, with permission, from reference 23.)

**Table 6: Authors' Recommended Indications for the Selective Use of FDG PET/CT with SSTR PET/CT**

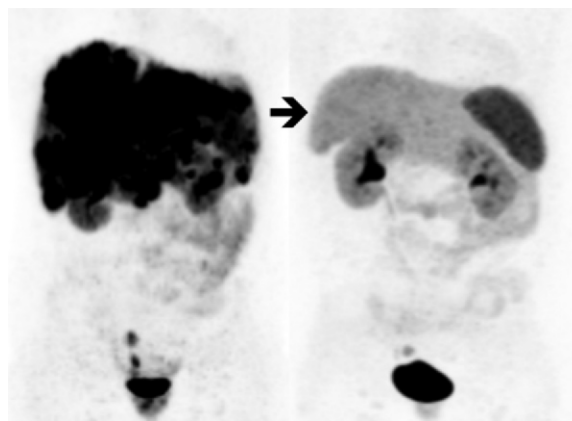
Ki-67  $\leq 5\%$

Worrisome lesions with little or no activity on the CT component of SSTR PET/CT

Clinical or radiologic evidence of disease progression within  $<6$  months despite Ki-67  $<5\%$

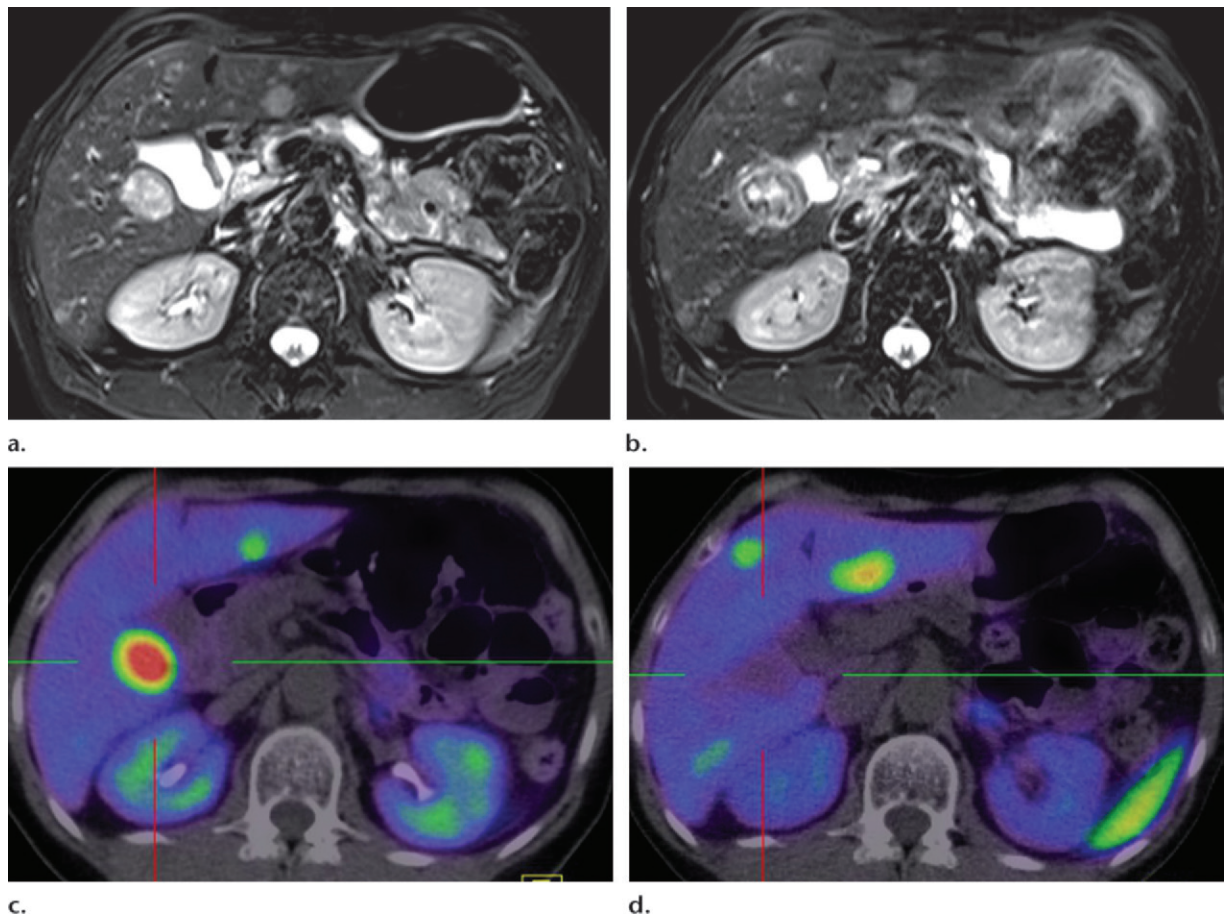
on coronal gray-scale PET images (Fig 9). However, this poses a potential pitfall for radiologists or physicians who are more experienced with octreotide imaging, with which this finding is rarely seen. Prominent islet cell clusters or islet cell hypertrophy can also occur elsewhere, resulting in heterogeneous low-grade pancreatic uptake. Mistaking exaggerated physiologic pancreatic uptake for pancreatic tumor can result in harmful consequences for the patient, especially if a Whipple procedure is performed on the basis of these findings. Close correlation with findings at MR imaging and thin-section multiphase CT can be helpful in further assessing equivocal findings.

**Spleen.**—Splenectomy is commonly performed in patients with pancreatic NET owing to the



**Figure 7.** High-grade (ENETS G3) metastatic rectal NET with locoregional nodal and diffuse hepatic metastases. GaTate PET/CT image (left) demonstrates high uptake at all sites, indicating suitability for PRRT. FDG PET/CT demonstrated intense metabolic activity consistent with a high-grade phenotype, but no sites of nontargetable FDG-avid discordant disease were noted. The patient received four cycles of  $^{177}\text{Lu}$ -DOTA-octreotate combined with radiosensitizing 5-fluorouracil. GaTate PET/CT image obtained 3 months later (right) shows near-complete response (arrow), corresponding to vast improvement in the patient's clinical status.

proximity of the spleen to the distal pancreas and the necessity of excising it when performing en bloc resection of the pancreatic tail. Splenosis is a common finding at restaging, and nodular sple-



**Figure 8.** ENETS G2 metastatic pancreatic NET with multiple hepatic metastases. The patient was treated with everolimus. (a) MR image demonstrates large hepatic metastases, including a segment V–VI lesion measuring 23 × 20 mm. (b) Restaging MR image obtained 3 months later demonstrates enlargement of the segment V–VI lesion to 31 × 25 mm, with a similar change in other metastases. (c, d) Pretreatment (c) and posttreatment (d) GaTate PET/CT images demonstrate complete functional response in the metastases. FDG PET/CT demonstrated similar findings. MR imaging defined progression on the basis of RECIST criteria, whereas functional imaging demonstrates that this phenomenon was due to cystic necrosis. By inaccurately defining progression, anatomic imaging may misinform management, since discontinuation of the effective agent would be considered.

**Table 7: Pitfalls of GaTate PET/CT**

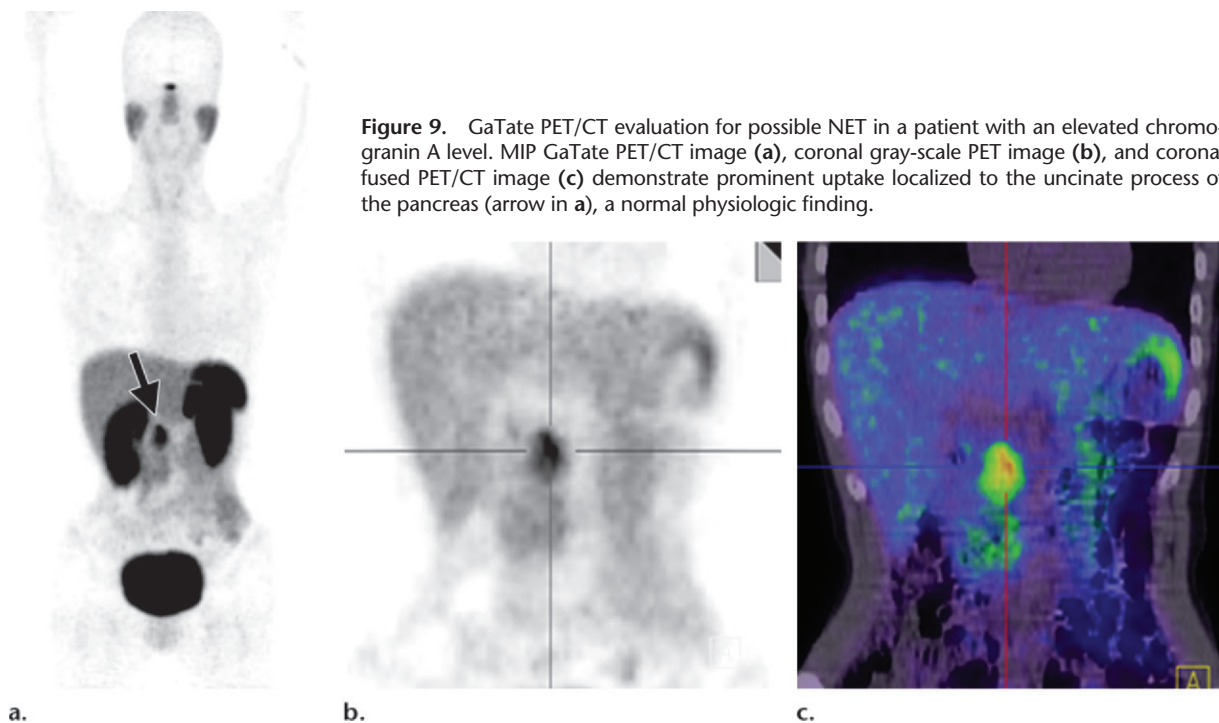
<b>Physiologic</b>
Pancreatic uncinate process activity
Splenuculi
<b>Osteoblastic</b>
Degenerative bone disease
Fracture
Vertebral hemangioma
Epiphyseal growth plates
<b>Inflammatory</b>
Reactive nodes
Prostatitis
Post–radiation therapy change
<b>Incidental</b>
Meningioma

nosis can be mistaken for peritoneal metastases at anatomic imaging and GaTate PET/CT because, like the normal spleen, these nodules demon-

strate very intense uptake (Fig 10). Thus, particularly in patients who undergo interval splenectomy, intense uptake in new, well-defined, round, peritoneal soft-tissue nodules may be due to splenosis. If there is uncertainty, denatured red blood cell SPECT/CT can help further characterize such lesions. In patients who do not undergo splenectomy, 80% of accessory spleens occur at the splenic hilum, although they may arise anywhere in the peritoneal cavity or within the pancreas. Splenuculi have lower-intensity uptake than the spleen ( $SUV_{max} \cong 11$  versus 29 for the spleen) (28), which may reflect a higher delivery rate of the peptide to the spleen due to its high arterial blood flow. Intrapancreatic splenuculus is another potential cause of false-positive GaTate PET/CT findings (29).

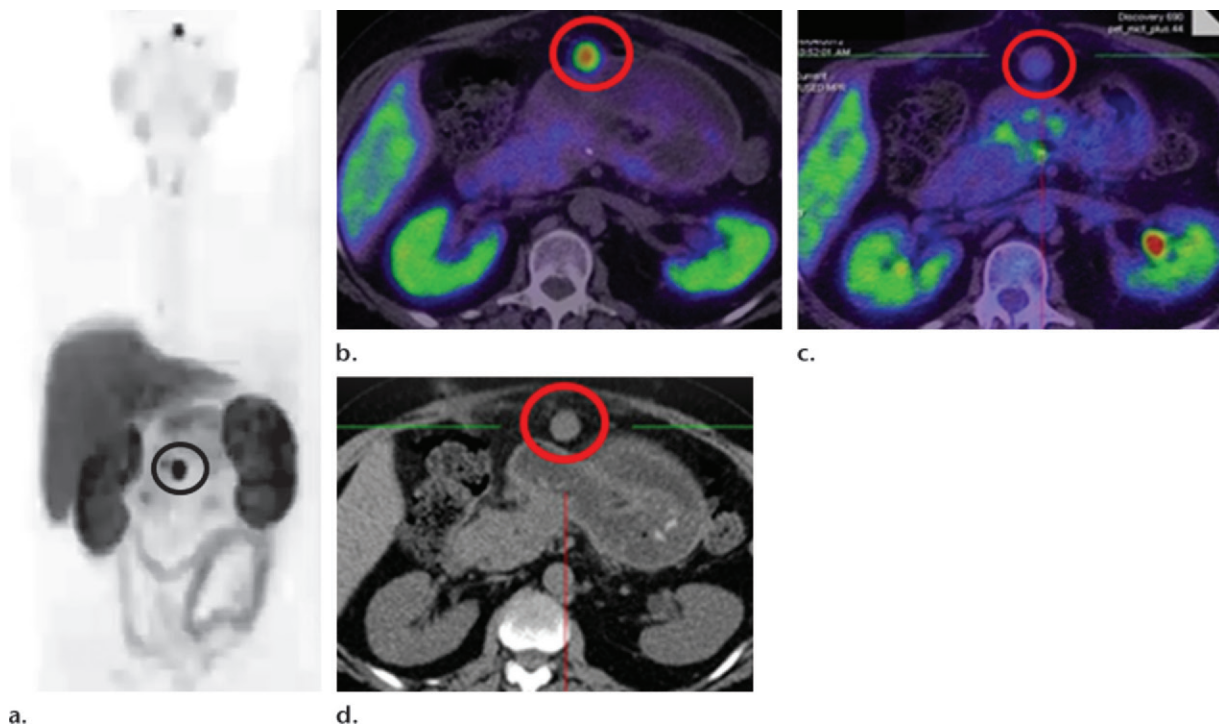
**Osteoblastic Activity**

Osteoblastic osseous processes demonstrate uptake at GaTate PET/CT, since osteoblasts express SSTR 2 (30). Degenerative bone disease,



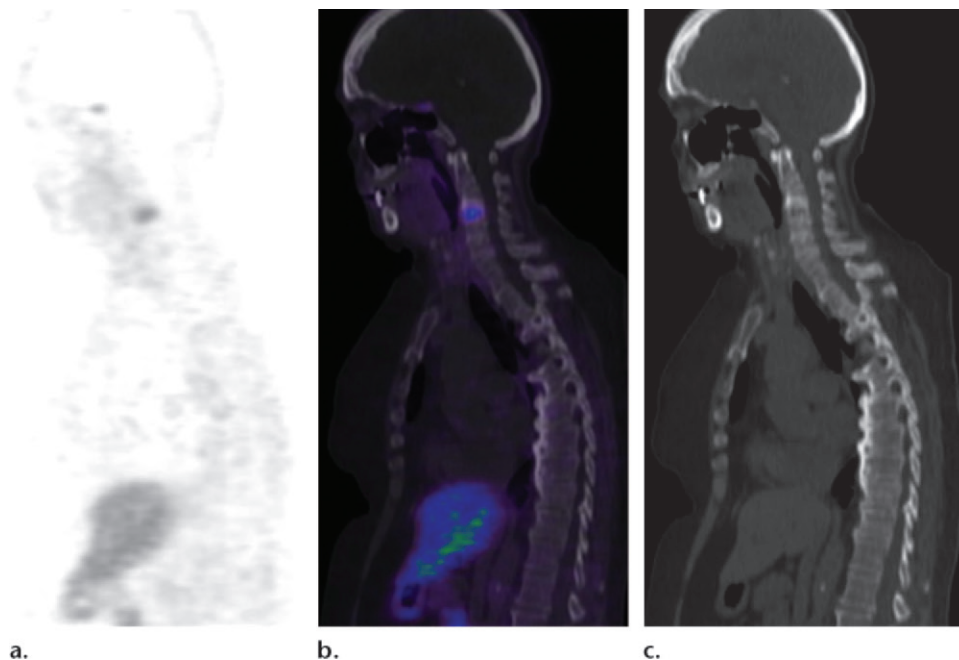
**Figure 9.** GaTate PET/CT evaluation for possible NET in a patient with an elevated chromogranin A level. MIP GaTate PET/CT image (a), coronal gray-scale PET image (b), and coronal fused PET/CT image (c) demonstrate prominent uptake localized to the uncinate process of the pancreas (arrow in a), a normal physiologic finding.

**Figure 10.** Splenosis in a patient who underwent distal pancreatectomy and splenectomy for excision of a NET. Restaging CT performed 3 months after surgery suggested a new peritoneal deposit. (a, b) MIP GaTate PET/CT image (a) and axial PET/CT image (b) show a 2-cm nodule (circle) with focal intense uptake. Note also the incidental finding of multiple meningiomas within the head on the MIP image. (c) FDG PET/CT image shows the nodule (circle) with only low uptake. (d) CT image shows the nodule (circle). Given the patient's history, the combined appearance of the nodule at GaTate PET/CT, FDG PET/CT, and conventional CT suggested a diagnosis of splenosis. Findings at denatured red blood cell SPECT/CT confirmed the diagnosis.



fractures, fibrous dysplasia, and vertebral hemangiomas (31,32) all demonstrate uptake, but these entities are readily distinguished from pathologic activity by virtue of their low- or very low-

intensity uptake and consistent features on the CT component of the study (Fig 11). Epiphyseal growth plates in children also demonstrate a low to moderate increase in activity.



**Figure 11.** Vertebral hemangioma. (a, b) Sagittal PET (a) and PET/CT (b) images show low-grade focal uptake in the C4 vertebral body. (c) CT image shows corresponding typical changes of a vertebral hemangioma. FDG PET/CT demonstrated a photopenic vertebral body.

### Inflammatory Processes

White blood cells including leukocytes and macrophages express SSTR 2, and some researchers have used this phenomenon to help image inflammatory processes such as atherosclerotic plaques with SSTR PET/CT (33). Inflammatory uptake is invariably low or very low grade and is most commonly seen in reactive hilar, mediastinal, axillary, or inguinal nodes. Inflammatory uptake is also commonly observed in prostatitis or post-radiation therapy change, although any inflammatory process may demonstrate some GaTate activity.

### Utility beyond Gastrointestinal NETs

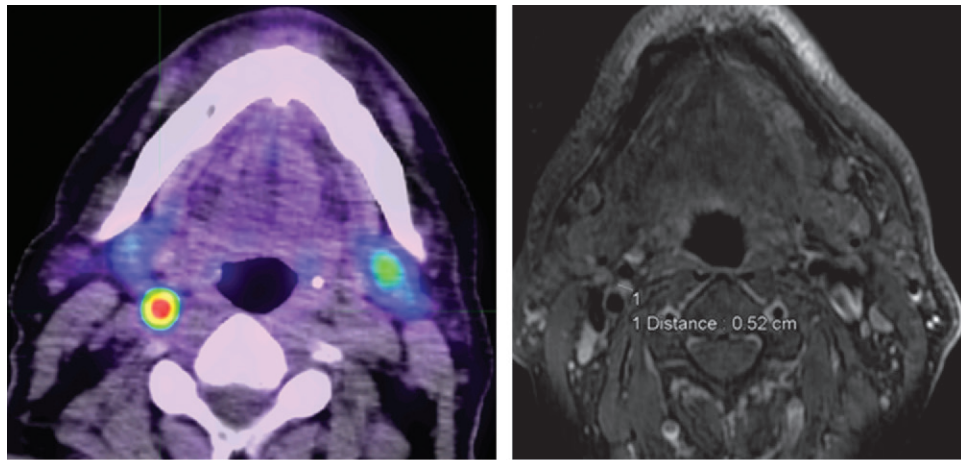
SSTR PET/CT also plays a major role in a number of other tumors with high levels of SSTR expression, including pheochromocytoma, paraganglioma, neuroblastoma, meningioma, and mesenchymal tumors causing oncogenic osteomalacia.

### Pheochromocytoma and Paraganglioma

Early experience with octreotide imaging demonstrated high uptake in neuroectodermal tumors, including pheochromocytoma and paraganglioma (34). Subsequently, iodine 123 ( $^{123}\text{I}$ )-metaiodobenzylguanidine (MIBG) became more commonly used in many centers for functional imaging. Our early experience with GaTate PET/CT suggests that it is the functional imaging modality of choice, and it has rapidly become our standard of care. In a small series of 12 patients with metastatic disease,

GaTate helped detect significantly more lesions with substantially higher tumor-to-background contrast than did  $^{123}\text{I}$ -MIBG (35). More recently, in a study of 62 patients with clinically suspected pheochromocytoma, GaNoc PET/CT had a sensitivity, specificity, and accuracy of 92%, 85%, and 90%, respectively, with 100% accuracy in 14 patients with multiple endocrine neoplasia type 2 (36). Its lesion-based accuracy (91%) was vastly superior to that for MIBG (67%); however,  $^{131}\text{I}$ -MIBG was used, which is inferior to  $^{123}\text{I}$ -MIBG.

The EANM 2012 guidelines for radionuclide imaging of pheochromocytoma and paraganglioma provide a complex system involving selective use of  $^{123}\text{I}$ -MIBG, fluorine 18 ( $^{18}\text{F}$ )-DOPA, FDG,  $^{111}\text{In}/^{68}\text{Ga}$  SSTR, or  $^{18}\text{F}$ -fluorodopamine, depending on genetic status and test availability (37). Our experience suggests that GaTate PET/CT is highly accurate across the range of mutations, including SDHx mutations, von Hippel-Lindau (VHL) mutations, multiple endocrine neoplasia type 2 (RET) mutations, and neurofibromatosis type 1 (NF1) mutations (Figs 12, 13). In contrast, other functional tests demonstrate uptake only in certain phenotypes. For example, FDG PET/CT demonstrates high uptake in SDHx-related disease owing to dysfunction of mitochondrial oxidative phosphorylation, but it typically demonstrates low uptake in RET/NF1-related disease. The high uptake of GaTate across the spectrum of disease suggests that GaTate PET/CT may be the best first-line investigation. MIBG SPECT/CT remains useful in assessment



**Figure 12.** Paraganglioma in a patient with intermittent headaches, paroxysmal sweats, and hypertension. Metanephrine levels were raised at conventional workup, which included CT and MIBG SPECT/CT, neither of which demonstrated any abnormality. **(a)** GaTate PET/CT image clearly depicts a paraganglioma at the carotid bifurcation. **(b)** Subsequently obtained MR image was initially thought to demonstrate normal findings, but a 5-mm nodule became apparent when the image was further reviewed with knowledge of the PET/CT findings.

of suitability for MIBG therapy, whereas GaTate PET/CT has allowed assessment for PRRT (38). SSTR-negative/ $^{18}\text{F}$ -DOPA-positive pheochromocytoma can occur (39), so that further imaging may be warranted in selected cases.

### Neuroblastoma

Our evolving experience indicates that GaTate PET/CT has greater sensitivity and specificity than  $^{123}\text{I}$ -MIBG SPECT/CT (40). We studied eight patients with refractory neuroblastoma and compared the results with pretreatment  $^{123}\text{I}$  or posttreatment  $^{131}\text{I}$  MIBG studies to assess concordance and degree of SSTR expression. GaTate PET/CT demonstrated high tumor-to-background contrast with a median  $\text{SUV}_{\text{max}}$  of 7, with additional sites of disease identified in five of 14 patients. Ten of 14 patients had sufficient SSTR expression to allow consideration of PRRT. The safety and feasibility of  $^{177}\text{Lu}$ -DOTATATE have also been demonstrated (41). The ability to complete an imaging study in a single session, combined with more rapid imaging with PET than with SPECT, is particularly beneficial in the pediatric population.

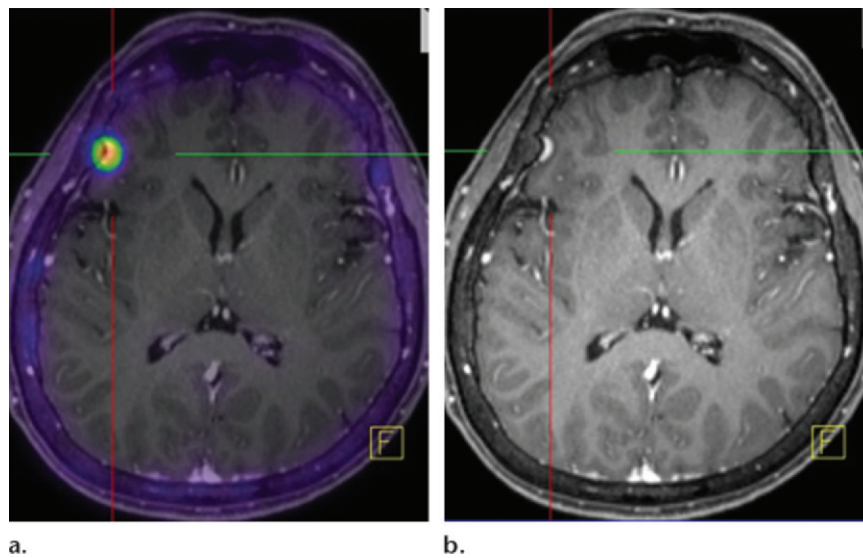
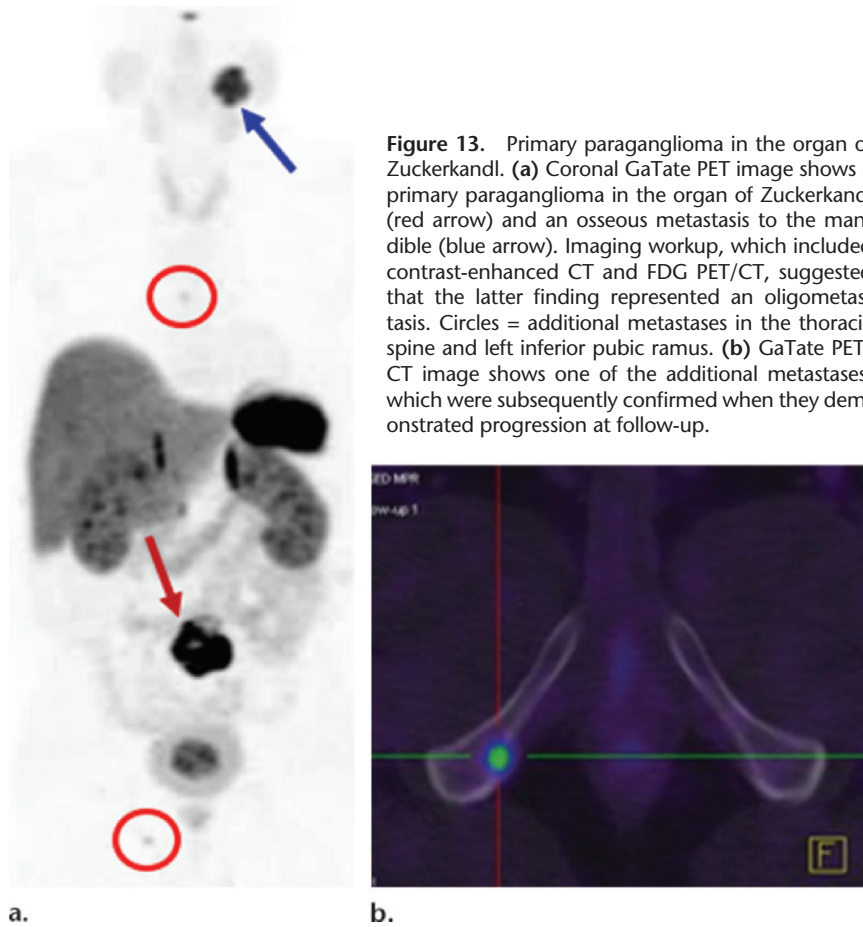
### Meningioma

Tiny incidental meningiomas are frequently visualized at GaTate PET/CT performed for other reasons (Fig 14). These subcentimeter lesions do not require further investigation but highlight the exquisite sensitivity and utility of GaTate PET/CT for the detection and characterization of meningioma. In a recent study of 134 patients, GaTate PET/CT was found to be superior to contrast-enhanced MR imaging, with 190

meningiomas being detected at PET compared with  $^{171}\text{Tl}$  at contrast-enhanced MR imaging (42). Furthermore, with knowledge of the PET/CT data, the MR imaging abnormalities could be visualized at only four of 19 sites (42). Tumors adjacent to the falx cerebri at the skull base or obscured by imaging artifacts or calcification were particularly difficult to visualize at MR imaging (42). Moreover, GaTate PET/CT is highly specific in characterizing abnormalities and is therefore useful if there is uncertainty as to whether an MR imaging finding represents a meningioma. In larger anaplastic meningiomas, the boundaries of involvement can be clearly defined at GaTate PET/CT (Fig 15). There is an increasing role for GaTate PET/CT or PET/MR imaging in improving the delineation of gross tumor volume for radiation treatment planning (43–45), often leading to a reduction in treatment volume compared with MR imaging or CT (46). There is also evidence that GaTate PET/CT can improve outcomes by helping identify patients who are likely to benefit from PRRT (47,48).

### Oncogenic Osteomalacia

Diagnosis of tumor-induced osteomalacia (TIO) has been significantly advanced with the introduction of GaTate PET/CT. TIO manifests with muscle weakness, bone pain, and recurrent fractures, resulting from renal phosphate wasting secondary to hormone secretion by the tumor, typically fibroblast growth factor 23 (FGF23). The presence of low serum phosphate levels and high urine phosphate levels should



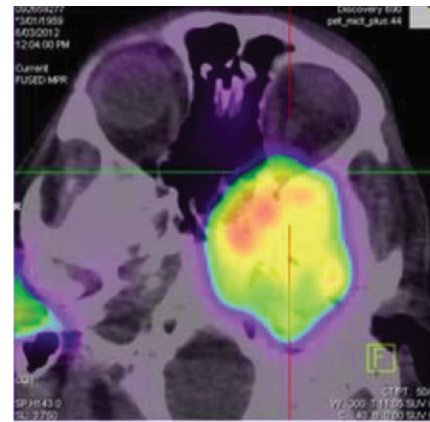
alert clinicians to this diagnostic possibility. Even when TIO is recognized, localization of causative tumors can prove difficult, since they are small, indolent, and often hidden in unusual locations, including the limbs, resulting in delayed diagnosis. We have shown that GaTate PET/CT is the imaging modality of choice for the diagnostic workup of TIO (Fig

16) (49). When GaTate PET/CT is performed for this purpose, it is critical to perform whole-body imaging that includes the upper and lower limbs in their entirety.

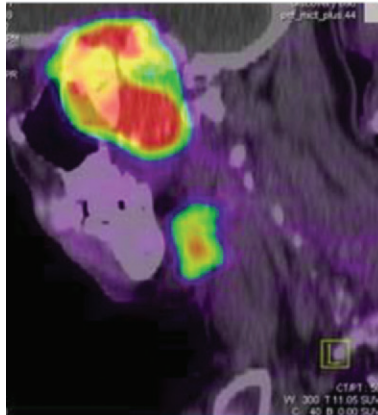
**Other Tumors**

There are a number of other tumors with variable SSTR expression in which GaTate PET/CT

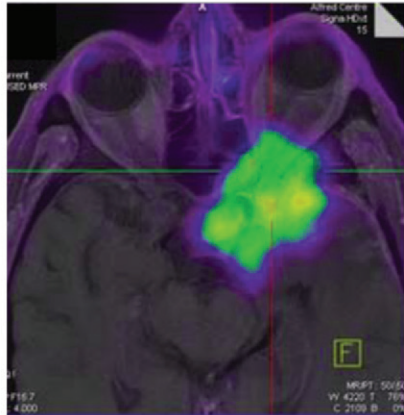
**Figure 15.** Anaplastic meningioma that had previously been treated with surgical debulking followed by radiation therapy. Several years later, the patient presented with altered vision. MR imaging demonstrated residual disease but provided no explanation for the visual disturbance. (a, b) Axial (a) and sagittal (b) GaTate PET/CT images clearly depict a mass. (c) Axial fused PET/CT-MR image shows the mass infiltrating the left optic nerve. (d) On an MR image, the boundaries of the mass are not clearly demarcated.



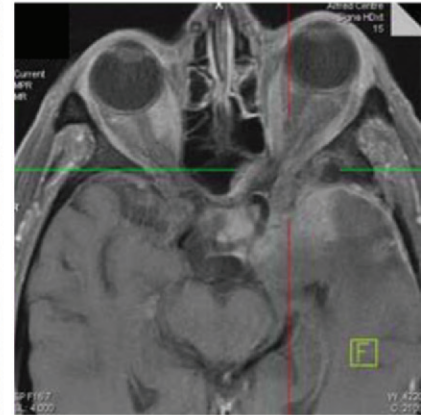
a.



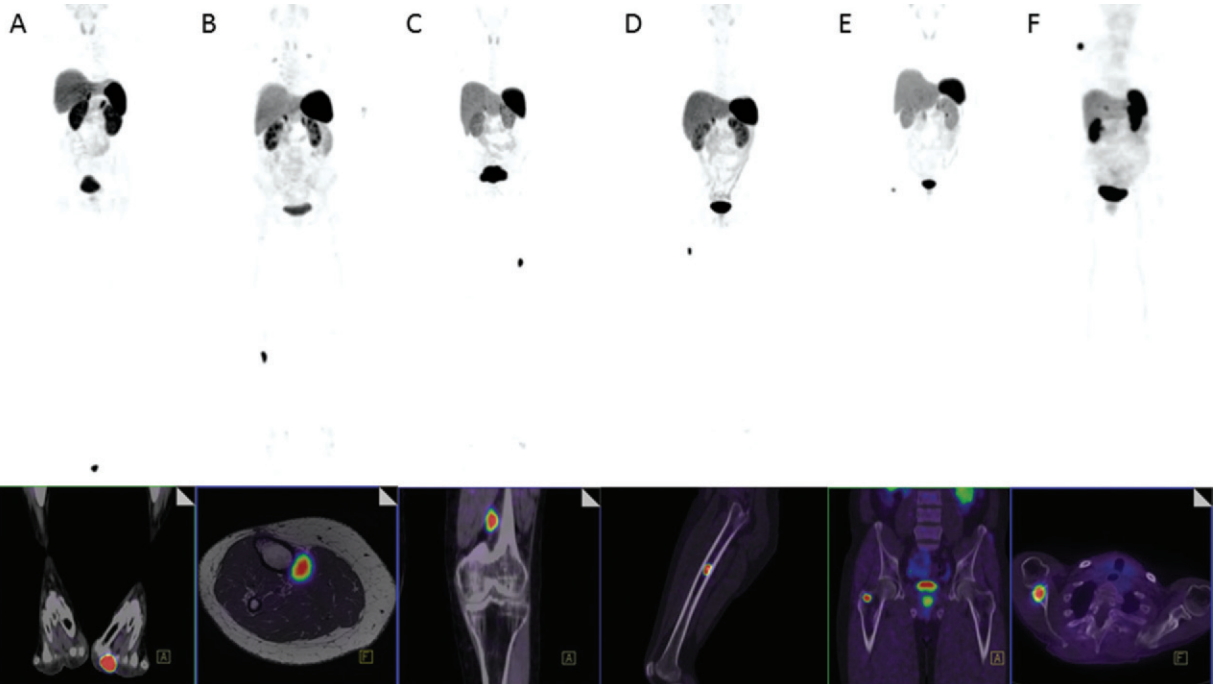
b.



c.



d.



**Figure 16.** TIO in six patients (A–F) who presented with widespread bone pain and muscle fatigue. All six patients had hyperphosphatemic hypophosphatemia and elevated fibroblast growth factor (FGF)-23 levels, and all six had a delayed diagnosis, either because the syndrome was not recognized or because the tumor could not be localized at conventional imaging. GaTate PET/CT allowed confident localization of the primary tumor in each patient (MIP GaTate PET/CT images [top], GaTate fused PET/CT and PET/MR images [bottom]). The tumor was subsequently excised in all cases. (Reprinted, with permission, from reference 49.)

has a role in both imaging and the evaluation of suitability for PRRT. These tumors include, but are not limited to, medullary thyroid cancer, Merkel cell carcinoma, small cell carcinoma, esthesioneuroblastoma, and iodine-negative thyroid cancer. The utility of GaTate PET/CT in other tumors has yet to be explored.

### Conclusion

GaTate PET/CT has an array of clinical applications in gastroenteropancreatic and other NETs, in which it is proving to represent a new standard of reference given its superior accuracy compared with conventional imaging techniques. The strength of GaTate PET/CT lies not only in its high sensitivity, but also in its ability to characterize whole-body SSTR expression, which confers a high specificity. This allows the selection of patients with metastatic disease for hormonal therapy or PRRT. FDG PET/CT plays a complementary role by helping identify sites of poorly differentiated disease on the basis of their higher proliferation rate. In selected patients, the use of both techniques can elegantly demonstrate tumor heterogeneity, which can be pivotal in guiding biopsy and selecting optimal management for individual patients.

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