



## <sup>68</sup>Gallium-DOTATATE positron emission tomography–computed tomography (PET CT) changes management in a majority of patients with neuroendocrine tumors ☆



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### ABSTRACT

**Background:** <sup>68</sup>Gallium-DOTATATE positron emission tomography–computed tomography (PET CT) has shown superior accuracy in detecting grade 1 and 2 neuroendocrine tumors over previous imaging modalities and was recently included in National Comprehensive Cancer Network guidelines. It remains unclear which patients benefit most from this imaging modality. We therefore reviewed our initial experience with <sup>68</sup>Gallium-DOTATATE PET CT to evaluate its usefulness in diagnosing, staging, and surveilling neuroendocrine tumors.

**Methods:** Records of patients who underwent <sup>68</sup>Gallium-DOTATATE PET CT from March to December 2017 were prospectively evaluated. The primary endpoint was whether <sup>68</sup>Gallium-DOTATATE PET CT changes treatment in patients with neuroendocrine tumors. Descriptive statistics, Fisher exact tests, and nested logistic regressions were conducted.

**Results:** A total of 50 consecutive patients were included. Of these, 41 patients (82%) had a biopsy-proven neuroendocrine tumor at the time of imaging. The remaining 9 patients (18%) had symptoms or biochemistry suggestive of a neuroendocrine tumor with negative cross-sectional imaging. <sup>68</sup>Gallium-DOTATATE PET CT changed management in 33 patients (66%). There were 24 patients with intermodality changes in management and 9 patients with intramodality changes in management. Patients with scans performed for staging had a higher likelihood of a change in management ( $P = .006$ ).

**Conclusion:** Performing <sup>68</sup>Gallium-DOTATATE PET CT should be considered for staging and surveillance of neuroendocrine tumors because it is frequently associated with changes in management.

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### Introduction

Neuroendocrine cells, which are peptide-producing cells found in many organs, can develop into a wide range of neuroendocrine tumors (NETs), including gastrointestinal, pancreatic, bronchial, lung, and thymic NETs, as well as medullary thyroid cancer, pheochromocytoma, and paraganglioma. The incidence of NETs has

been steadily increasing over recent decades and has recently been reported to be as high as 5.86 per 100,000.<sup>1</sup> These tumor types were previously thought to be relatively indolent, but gastrointestinal and pancreatic NETs are now known to present with distant metastases at the time of diagnosis in 40%–50% of cases.<sup>2</sup>

Traditional anatomic imaging via computed tomography (CT), ultrasound, or magnetic resonance imaging (MRI) has been supplemented in NETs with <sup>111</sup>In-DTPA-pentetreotide (Octreoscan), which uses a radiolabeled somatostatin analogue to bind somatostatin receptors 2 and 5, expressed on NET cells.<sup>3</sup> Octreoscan is limited by low image quality, high radiation dose, and a 24-hour imaging protocol.<sup>3,4</sup> Other functional imaging modalities, including fluorodeoxyglucose positron emission tomography scan, are ineffective

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at detecting well-differentiated and moderately differentiated NETs because of the near-normal glucose turnover of these tumors.<sup>5</sup>

<sup>68</sup>Gallium-DOTATATE PET CT (<sup>68</sup>Ga-DOTATATE PET CT) uses a radiolabeled somatostatin analogue to bind somatostatin receptor-2, which is expressed on the surface of well-differentiated and moderately differentiated NETs. Unlike Octreoscan, it combines functional and anatomic imaging to produce a higher quality image with anatomic correlation of somatostatin receptor expression. It has been used widely in Europe since the early 2000s, was included in the most recent National Comprehensive Cancer Network guidelines, and was approved for use in the United States by the Food and Drug Administration (FDA) in 2017.<sup>6</sup> Its advantages over Octreoscan include a radiation dose of  $2.57 \times 10^{-2}$  mSV/MBq, 3 to 5 times lower than Octreoscan; a 45-minute scanning protocol; and the ability to superimpose functional imaging on a thick-cut CT scan.<sup>7,8</sup> Although <sup>68</sup>Ga-DOTATATE PET CT has been shown in multiple studies to be more accurate at detecting grade 1 and 2 NETs than Octreoscan, the precise indications for use of <sup>68</sup>Ga-DOTATATE PET CT were not specified in the National Comprehensive Cancer Network guidelines.<sup>7,9,10</sup>

The initial experience with <sup>68</sup>Ga-DOTATATE PET CT at this tertiary care academic medical center was therefore reviewed to evaluate its usefulness in diagnosing, staging, and restaging NETs. This study also examines whether specific patient or tumor factors predicted a change in treatment management after the scan.

## Methods

Rush University Medical Center is a 664-bed, tertiary care academic referral hospital located in Chicago, Illinois, with a multidisciplinary NET center. Rush University Medical Center obtained access to <sup>68</sup>Ga-DOTATATE PET CT imaging in March 2017 as the first center in Illinois after the FDA approved it 6 months earlier.

A database of 50 patients undergoing <sup>68</sup>Ga-DOTATATE PET CT imaging from March to December 2017 was prospectively compiled. Patient records were then retrospectively reviewed for demographics, tumor characteristics, primary tumor site, scan indication, results, and postscan management. Occult primary tumors were defined as biopsy-proven NETs with known metastatic disease (eg, in the liver) but without a known primary tumor site. Patients were considered to have suspected NETs if they had symptoms or elevated biochemical markers (eg, chromogranin A or metanephrines) consistent with a NET or pheochromocytoma. Whether treatment was changed was determined by chart review comparison before and after the scan. Changes in management were further classified as intermodality changes (a change from 1 treatment modality to another [eg, surgery to systemic therapy]) or intramodality changes (a change within a treatment modality [eg, change in extent of surgery or from 1 chemotherapy agent to another]).

Indications for ordering <sup>68</sup>Ga-DOTATATE PET CT included detection of an occult primary tumor, staging or surveillance, classification of an indeterminate lesion, elevated serum biomarkers, or NET-related symptoms. Surveillance and staging were treated as 1 indication because all but 1 patient had never undergone <sup>68</sup>Ga-DOTATATE PET CT and, therefore, were being restaged with the new technology as opposed to undergoing surveillance with other imaging modalities. Systemic therapies included somatostatin analogues, everolimus, sunitinib, capecitabine/temozolamide, and <sup>177</sup>Lutetium Peptide Receptor Nucleotide Therapy (PRRT).

All patients had at least 1 anatomic imaging modality (CT or MRI), within 6 months before <sup>68</sup>Ga-DOTATATE PET CT, which was used for comparison. The scan protocol was standardized by radiology. A total of  $5.4\text{mCi} \pm 10\%$  <sup>68</sup>Ga-DOTATATE was administered into a peripheral vein 45 minutes before total body imaging with a dedicated PET-CT scanner. Each patient was scanned from the

skull base to the mid thigh and the scan was read by 1 of 2 board-certified nuclear medicine physicians. False positive scans were defined as those that detected somatostatin-avid lesions that were later found to not be NETs on pathology.

All patients underwent biochemical workup before <sup>68</sup>Ga-DOTATATE PET CT, including determination of chromogranin A or plasma serotonin or urinary 5-HIAA levels. Symptoms attributed to a NET included diarrhea, flushing, wheezing, palpitations, blurry vision, and refractory hypertension in patients with suspected paraganglioma or pheochromocytoma.

Descriptive statistics were calculated for age, sex, primary tumor location, tumor grade, tumor stage, indication for <sup>68</sup>Ga-DOTATATE PET CT, whether the patient had prior functional imaging, the number of patients who had a change in management, the number with new lesions, and the number whose suspicious lesions were found to not be somatostatin-avid.

Fisher exact tests were used to assess whether the following variables were associated with change in treatment management: tumor grade, tumor stage, the presence of known liver metastases, primary site of the tumor, indication for <sup>68</sup>Ga-DOTATATE PET CT, and whether the patient had prior functional imaging. Nested logistic regression models were created with pre-imaging variables that were significant by Fisher exact tests. These models were compared with likelihood ratio tests. All analyses were conducted in R 3.3.2.<sup>11</sup> The study was approved by the Rush University Medical Center Institutional Review Board. Consent and Health Insurance Portability and Authorization Act authorization were waived because the study presented no more than minimal risk and used data collected solely for clinical purposes.

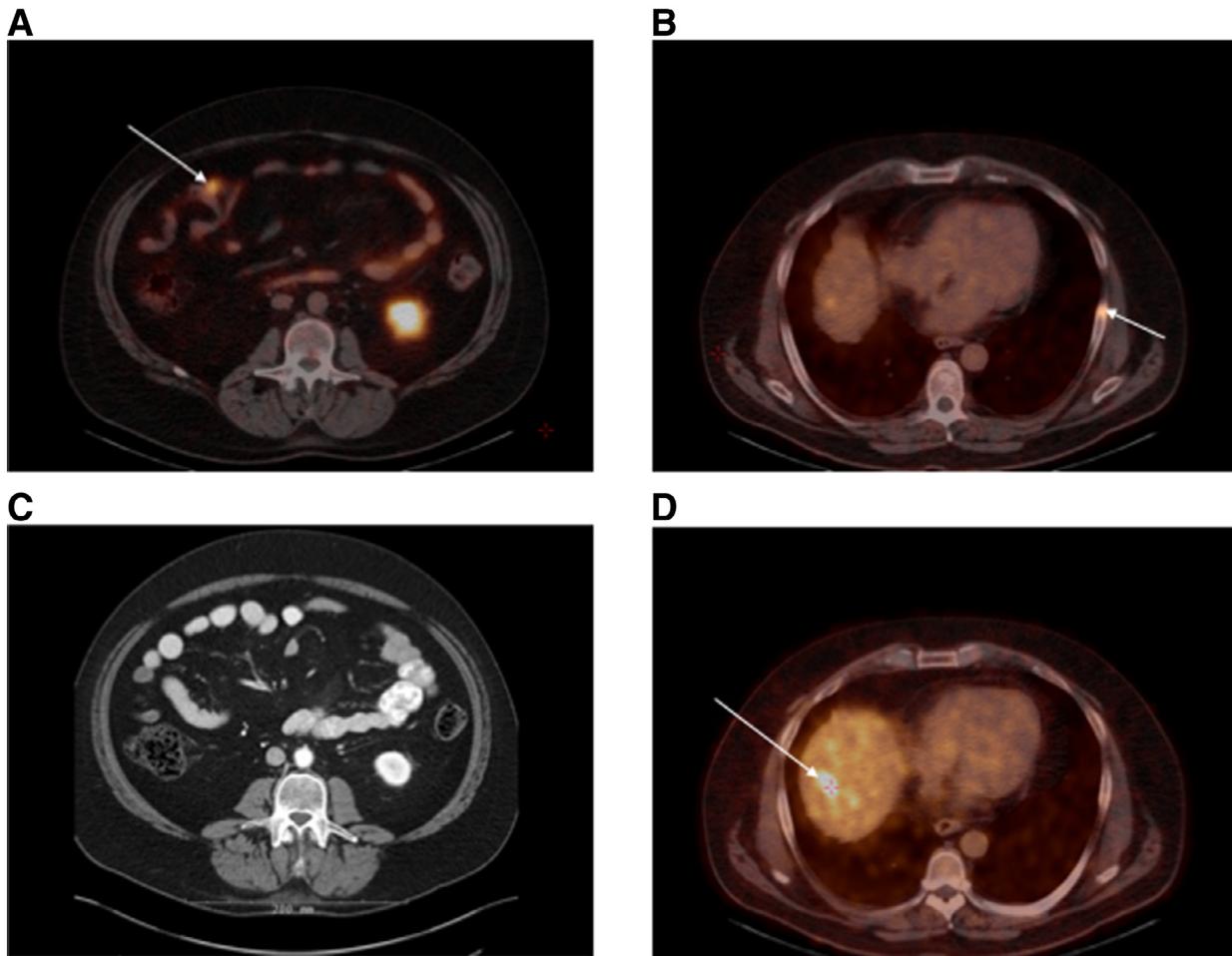
## Results

In total, 50 consecutive patients were included, of whom 32 (64%) were female. Median age was 59.5 years, with a standard deviation of 10.1 years. There were 41 patients (82%) with a histologically proven NET at the time of imaging. The most common primary tumor location was small intestine (15 patients), followed by pancreas (8 patients). A total of 5 patients had histologic confirmation of a metastatic NET with an occult primary tumor.

At the time of imaging, 9 patients (18%) had suspected NETs because of elevated biochemical markers, symptoms, or both elevated biochemical markers and symptoms, with no tissue diagnosis and negative cross-sectional imaging. Of these patients, 4 had greater than 2-fold elevated metanephrines and refractory hypertension, suspicious for pheochromocytoma or paraganglioma; the remainder had carcinoid symptoms, including 3 patients with elevated chromogranin A. Additional tumor characteristics can be found in Table 1. The most common indication for <sup>68</sup>Ga-DOTATATE PET CT was tumor staging or surveillance (30 patients, 60%; Table 2).

<sup>68</sup>Ga-DOTATATE PET CT changed management in 33 patients (66%). Intermodality changes in management occurred in 24 patients (73%). Intramodality changes in management occurred in 9 patients (27%; Table 3).

Of the patients who had an intermodality change in management, 9 patients who were previously under consideration for resection were directed to somatostatin analogues (5), Yttrium-90 radioembolization (2), PRRT (1), or surveillance (1). Of these patients, 7 were found to have either extrahepatic metastases or more extensive liver disease than previously known; the remaining 2 had less disease than previously suspected (Fig. 1). Because of the recognition that an operation could achieve an adequate tumor debulking threshold without leaving significant tumor burden in situ, 3 patients with intermodality changes in management were transitioned from systemic therapy to operative



**Fig. 1.** Example of a patient with an occult primary tumor and liver metastases who had previously undergone several rounds of liver-directed Yttrium-90 treatment.  $^{68}\text{Ga}$ -DOTATATE positron emission tomography–computed tomography (PET CT) revealed a small intestinal primary; new rib, scapula, and vertebral metastases; and the known liver metastasis (A, B, D). Neither the primary tumor nor the bone metastases were symptomatic or seen on CT scan (C). He was then referred for  $^{177}\text{Lu}$  Lutetium Peptide Receptor Nucleotide Therapy (PRRT) because of the small amount of liver disease in a patient who had previously undergone liver-directed therapy, and the larger burden of skeletal metastases. This represents an intermodality change, from planned surgical resection to PRRT.

management of liver metastases based on  $^{68}\text{Ga}$ -DOTATATE PET CT findings (Fig. 2).

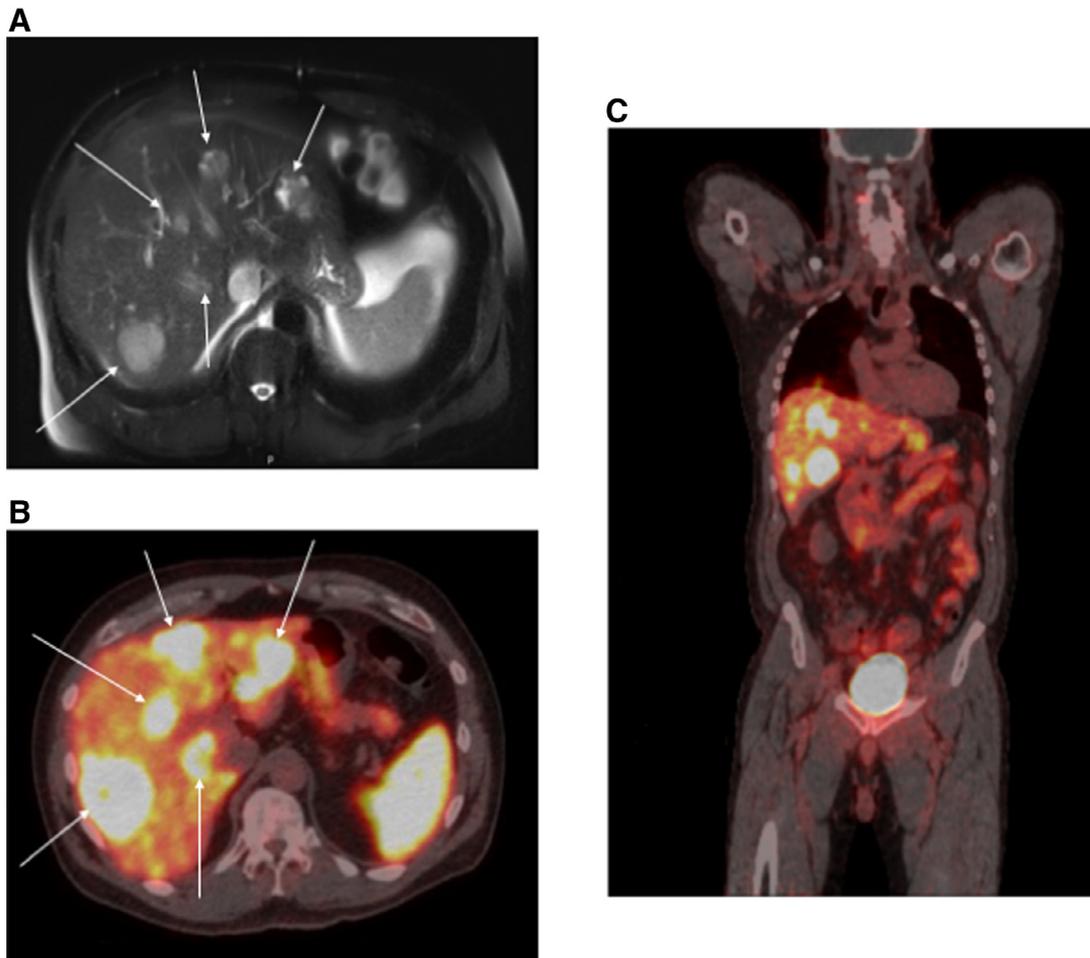
In total, 4 of the 9 intramodality changes in management represented changes in operative planning to include additional liver lesions not seen on cross-sectional imaging or newly discovered occult primary tumors (Fig. 3). The other 5 intramodality changes in management represented changes in surveillance strategies in patients who were discovered to have suspicious lesions that required additional workup. Of these patients, 4 underwent MRI of suspicious bone lesions and 1 underwent endoscopy for a suspicious stomach lesion. Bone metastases were discovered in 2 patients on MRI.

On univariate analysis, indication and the presence of previously known liver metastases were associated with the scan changing treatment management ( $P = .02$  and  $.03$ , respectively). On multivariate analysis,  $^{68}\text{Ga}$ -DOTATATE PET CT was significantly more likely to be associated with a change in management if it was performed for staging or surveillance compared to other indications (OR 6.5, CI 1.7–24.7,  $P = .006$ ). There was no significant relationship between tumor grade, tumor stage, the primary site of the tumor, or previous functional imaging and change in management after  $^{68}\text{Ga}$ -DOTATATE PET CT ( $P$  values ranged from .43 to .99).

New lesions were detected in 27 patients (54%; Table 4; Figs. 1–4). Lesions suspicious for disease on anatomic imaging

were not  $^{68}\text{Ga}$ -DOTATATE PET CT-avid in 6 patients (19%). Of the 5 occult primary tumors (40%), 2 were located by  $^{68}\text{Ga}$ -DOTATATE PET CT; both were found in the small intestine. None of the 9 scans performed for diagnosis in patients with biochemical markers or symptoms suggestive of a NET showed  $^{68}\text{Ga}$ -DOTATATE avidity. It was recommended that 10 patients (20%) undergo an operation after  $^{68}\text{Ga}$ -DOTATATE PET CT. Recurrence was detected in 3 of 5 patients (60%) who had previously undergone curative resection and were thought to be disease-free at the time of  $^{68}\text{Ga}$ -DOTATATE PET CT based on biomarkers, cross-sectional imaging, and symptoms. All 3 patients experienced a change in management.

False positive lesions were found in 2 patients (4%) on  $^{68}\text{Ga}$ -DOTATATE PET CT. The first patient had carcinoid-like symptoms with negative cross-sectional imaging and normal biomarkers. A somatostatin-avid lesion on  $^{68}\text{Ga}$ -DOTATATE PET CT was detected in fundus of the stomach; endoscopy revealed a polyp without NET features or dysplasia on biopsy. The second patient was thought to have a pancreatic NET on CT but had an equivocal endoscopic ultrasound-guided biopsy. She had a negative  $^{99}\text{Tc}$  Sulfur scan for splenule and subsequently underwent  $^{68}\text{Ga}$ -DOTATATE PET CT, which demonstrated uptake in the pancreatic tail, corresponding with the lesion on CT. Laparoscopic distal pancreatectomy was performed, but pathology revealed an intrapancreatic accessory spleen.



**Fig. 2.** Example of a patient with a grade 1, stage IV ileal neuroendocrine tumor (NET) who had previously undergone resection of both the primary tumor and segment I liver metastases and who was found to have extensive liver metastases on surveillance magnetic resonance imaging (MRI) (A).  $^{68}\text{Ga}$ -DOTATATE PET CT was performed to evaluate the patient for potential  $^{177}\text{Lu}$  Lutetium Peptide Receptor Nucleotide Therapy (PRRT) treatment. He was found to have disease limited to the liver amenable to debulking without extrahepatic disease (B, C) and underwent multiple parenchymal sparing liver resections and intraoperative tumor ablations. This represents an intermodality change, from planned PRRT to surgical resection.

## Discussion

Of the patients who underwent  $^{68}\text{Ga}$ -DOTATATE PET CT, 66% experienced changes in management, and 54% had new lesions detected. Specific factors associated with a change in treatment plan after  $^{68}\text{Ga}$ -DOTATATE PET CT included the presence of known liver metastases and the scan being performed for staging or surveillance.

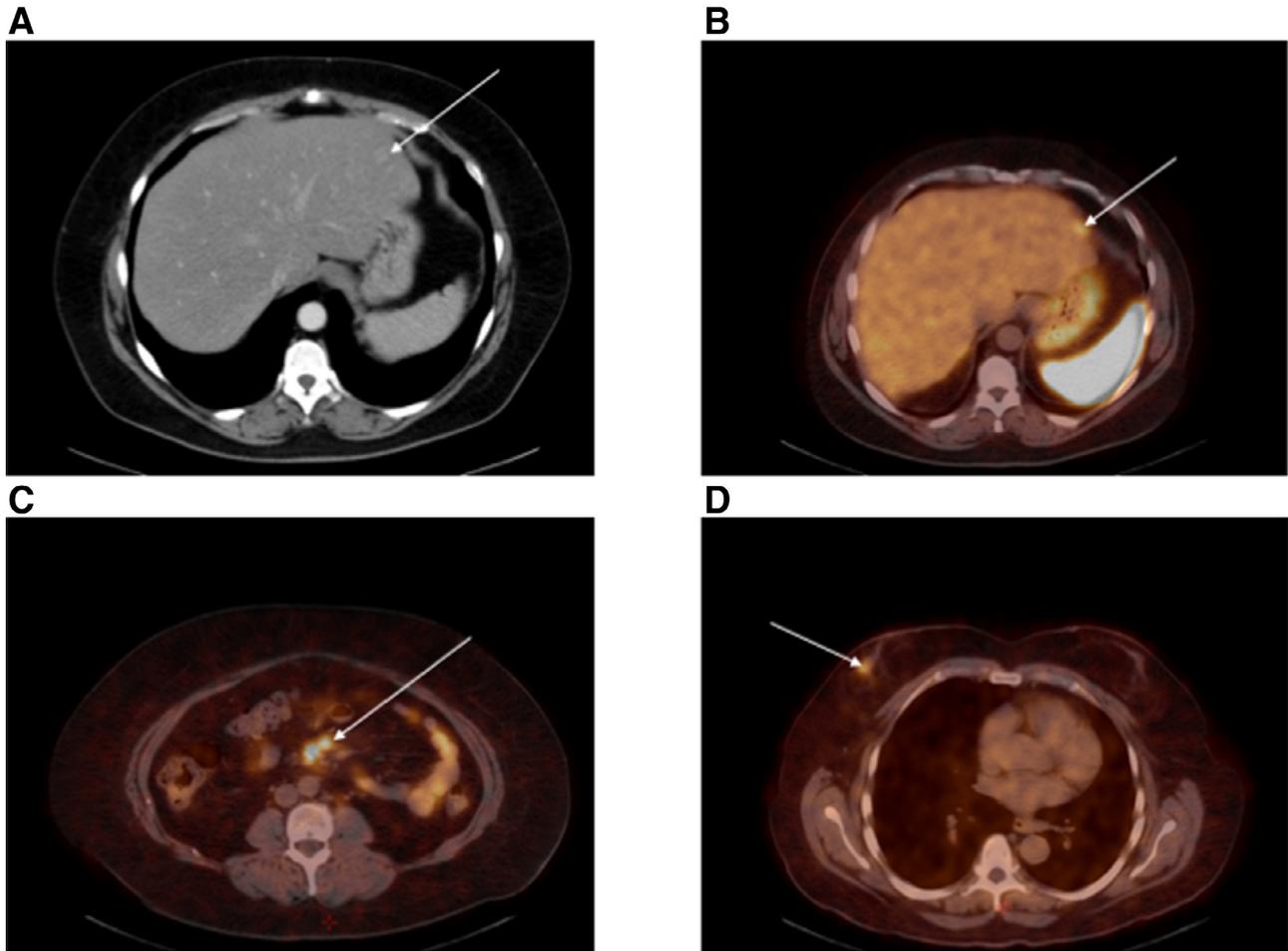
Previous studies have found that  $^{68}\text{Ga}$ -DOTATATE PET CT changes treatment plans in 16–71% of patients.<sup>6,7,9,12</sup> The largest published series of  $^{68}\text{Ga}$ -DOTATATE PET CTs, which consists of 1,258 scans since 2005 in 728 patients in the United Kingdom, reports change in management in 40.9% of patients.<sup>12</sup> That rate is lower than the rate of treatment changes reported here, possibly owing to the relatively high number of patients who underwent multiple  $^{68}\text{Ga}$ -DOTATATE PET CT scans in that study. All patients in our study were undergoing their first  $^{68}\text{Ga}$ -DOTATATE PET CT at this center, unlike many European studies, which include patients who receive regular  $^{68}\text{Ga}$ -DOTATATE PET CT scans for surveillance. Because change in management depends on clinicians' perception of disease burden, it is possible that  $^{68}\text{Ga}$ -DOTATATE PET CT is more likely to alter management the first time it is used.

A meta-analysis found that intermodality changes in management occurred in 77% of patients whose management changed after  $^{68}\text{Ga}$ -DOTATATE PET CT, similar to the 73% rate reported here.<sup>6</sup>

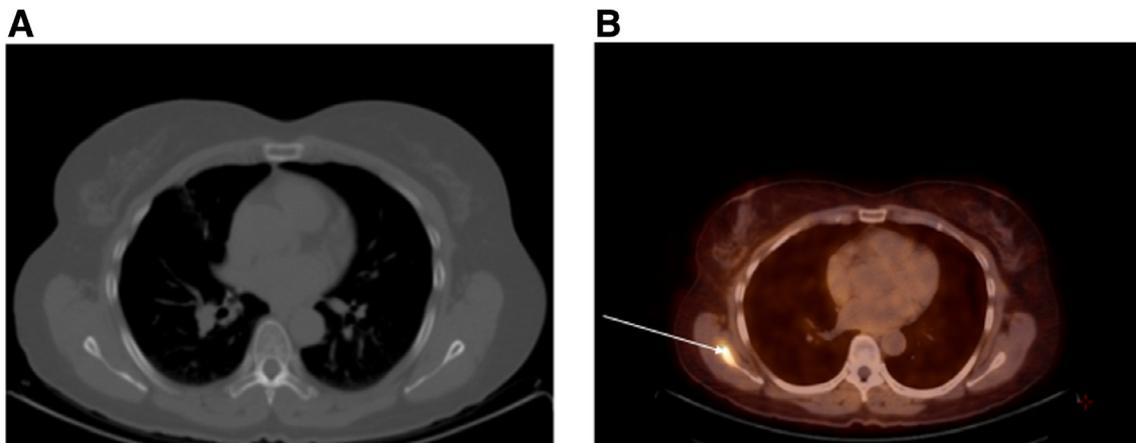
Patients were 3 times more likely to be referred from operative to nonoperative management based on their scan results as vice versa.  $^{68}\text{Ga}$ -DOTATATE PET CT's ability to reveal new metastatic sites that lead clinicians to consider a patient to be a better candidate for medical management, as illustrated by the case in Fig. 1, likely contributes to the high rate of intermodality changes in management.

The superiority of  $^{68}\text{Ga}$ -DOTATATE PET CT over Octreoscan was demonstrated in a prospective study of 131 patients who underwent both imaging modalities. In total, 95% of known neuroendocrine lesions were detected by  $^{68}\text{Ga}$ -DOTATATE PET CT compared with 45% for anatomic imaging and 30.9% for Octreoscan.<sup>9</sup> Lesions were detected in 65% of patients with carcinoid symptoms and negative biochemical testing; 40% of these lesions were not detected by other imaging.<sup>9</sup> Comparison with Octreoscan was not possible with our cohort because relatively few patients underwent Octreoscan within 1 year of  $^{68}\text{Ga}$ -DOTATATE PET CT.

The rate of false positive results in this study was found to be 4%, slightly higher than the 1.1% reported in the largest  $^{68}\text{Ga}$ -DOTATATE PET CT series and the 1.2% reported in the initial efficacy study in the United States.<sup>7,12</sup> The rate remains low, however, and will likely decrease with a larger sample size. False positives were classified on a patient level, and not on a lesion level, because many lesions were never biopsied. It was recognized that some somatostatin-avid lesions, such as a thyroid nodule and



**Fig. 3.** Example of a patient with a previously resected small intestinal NET who had postoperative persistent mild lymphadenopathy thought to be reactive, as well as a liver segment 3 lesion thought to be a hemangioma (A).  $^{68}\text{Ga}$ -DOTATATE positron emission tomography–computed tomography (PET CT) showed a somatostatin-positive lesion in the left lobe of the liver (B) and multiple avid mesenteric lymph nodes with a possible recurrence at the anastomotic site (C). She was also incidentally found to have somatostatin-avid lesions in the breast and axilla (D); further workup revealed invasive ductal carcinoma of the breast. She underwent treatment of her breast cancer, followed by re-resection of the anastomosis, mesenteric lymph nodes, and segment 3 liver lesion. All lesions were confirmed to be NET on final histopathology. This represents an intramodality change, as the operation now included a liver resection.



**Fig. 4.** Example of a patient with a completely resected stage 1, grade 2 atypical lung carcinoid who had no evidence of disease recurrence on anatomical imaging 1 year after surgery (A). A  $^{68}\text{Ga}$ -DOTATATE positron emission tomography–computed tomography (PET CT) performed for surveillance found an isolated lesion in her right scapula suggestive of a metastasis (B) that was not seen on the corresponding computed tomography (CT) scan (A). She underwent percutaneous microwave ablation of this isolated lesion by interventional radiology. This represents an intermodality change, from somatostatin antagonist to microwave ablation.

**Table 1**  
Patient and tumor characteristics, as known prior to <sup>68</sup>Ga-DOTATATE PET CT

Patient / tumor characteristic	Number of patients (n = 50) (%)
Primary tumor site	
Small intestine	15 (30)
Pancreas	8 (16)
Occult primary	5 (10)
Rectum	4 (8)
Stomach	3 (6)
Lung	3 (6)
Colon	1 (2)
Thymus	1 (2)
Liver teratoma	1 (2)
Suspected NET without diagnosis	9 (18)
Symptoms only*	2 (4)
Biochemical markers only*	2 (4)
Symptoms and biochemical markers*	5 (10)
Grade	
Grade 1	22 (44)
Grade 2	15 (30)
Grade 3	0
Stage	
Stage I	8 (16)
Stage II	3 (6)
Stage III	6 (12)
Stage IV	24 (48)
Liver metastases	20 (40)
Functional tumors	29 (58)
Prior functional imaging	13 (26)

\* These patients had no evidence of a neuroendocrine tumor on cross-sectional imaging.

**Table 2**  
Indication for <sup>68</sup>Ga-DOTATATE PET CT

Indication	Number of patients (n = 50) (%)
Staging/surveillance	30 (60)
Symptoms	10 (20)
Elevated biomarkers	10 (20)
Indeterminate lesion	7 (14)
Occult primary tumor	5 (10)

Note: Patients could have multiple indications for <sup>68</sup>Ga-DOTATATE PET CT (ie, surveillance plus elevated biochemical profile).

**Table 3**  
Management after <sup>68</sup>Ga-DOTATATE PET CT was performed

Change in management	Number of patients (n = 50) (%)
Total change in management	33 (66)
Intermodality change in management	24 (48)
Surgery	3 (6)
Medical management (eg, somatostatin antagonist)	7 (14)
PRRT	6 (12)
Yttrium-90 radioembolization	4 (8)
Surveillance	2 (4)
Percutaneous microwave ablation	2 (4)
Intramodality change in management	9 (18)
Change in extent of surgery	4 (8)
Change in type of surveillance	5 (10)

**Table 4**  
Location of newly detected lesions on <sup>68</sup>Ga-DOTATATE PET CT

Location	Number of patients (n = 50) (%)
Liver	11 (22)
Bone	9 (18)
Mesenteric lymph nodes	8 (16)
Abdominal wall / soft tissue	6 (12)
Small intestine	3 (6)
Lung	3 (6)
Thoracic lymph nodes	3 (6)

breast mass, were unlikely to be NETs, but still required additional workup; these were not considered false positives. A prior series of patients with NETs who underwent <sup>68</sup>Ga-DOTATATE PET CT found that 11% of patients had somatostatin uptake in the thyroid; 3 of these 28 patients were later found to have papillary thyroid cancer.<sup>13</sup> Physiologic uptake can be found in other organs expressing somatostatin receptors, such as the spleen, adrenal, pituitary, as well as the uncinata process and head of the pancreas.<sup>3,7</sup> Physiologic uptake in the pancreas (especially the uncinata process) is a particular area of concern, as somatostatin receptors are primarily expressed in islet cells, which can give the appearance of focal uptake and therefore be misinterpreted as a tumor.<sup>14</sup>

The rate of false negative results was 2%, consistent with the rate of 2.3% reported in the largest series. It is unclear whether any of the 9 patients with clinical suspicions for a NET and a negative <sup>68</sup>Ga-DOTATATE PET CT will eventually be found to have a NET.

Up to 35% of patients with symptoms, biomarkers, or imaging suspicious for NETs without a tissue diagnosis have been reported to have a NET detected on <sup>68</sup>Ga-DOTATATE PET CT, and detection rates for pheochromocytoma and paraganglioma have been reported to be up to 96%–98%.<sup>15–18</sup> Guidelines from the Society of Nuclear Medicine and Molecular Imaging have proposed that the use of <sup>68</sup>Ga-DOTATATE PET CT is appropriate in patients with biochemical evidence and symptoms of NET without evidence of a tumor on cross-sectional imaging because a negative scan could potentially exclude a NET diagnosis.<sup>19</sup> None of the 9 scans performed for diagnosis in this study—including those performed for patients with suspected pheochromocytoma—resulted in a true positive, although negative scans in 3 patients were considered sufficient evidence to exclude a NET diagnosis. The patients in this study with negative cross-sectional imaging and <sup>68</sup>Ga-DOTATATE PET CT but positive biochemical markers could have had falsely elevated biochemical workups that led us to believe they had NETs or pheochromocytomas. Further study, including a larger sample size, is necessary to evaluate whether <sup>68</sup>Ga-DOTATATE PET CT should be obtained in a patient with symptoms, cross-sectional imaging, or elevated biomarkers suspicious for NET.

<sup>68</sup>Ga-DOTATATE PET CT has been reported to detect NET recurrences in 46% of patients who have previously undergone resection with no evidence of residual disease and in 27% of the subgroup of patients who had no suspicion of recurrence.<sup>20</sup> Undiscovered disease was found in 3 of the 5 patients who had undergone prior resection with no clinical suspicion of disease at the time of scanning, and all 3 of these patients subsequently experienced a change in management. This high rate of asymptomatic recurrence in previously resected patients perhaps suggests that patients should consider undergoing regular surveillance with <sup>68</sup>Ga-DOTATATE PET CT, although the precise indications and timing of surveillance warrants further investigation.

Limitations of this study include its retrospective nature, the necessarily small sample size for a new technology recently approved by the FDA, and the blurring of the distinction between staging, restaging, and surveillance indications. Although all patients had anatomic imaging, only one quarter had recent functional imaging, so direct comparison with Octreoscan was not possible. In addition, the short length of follow-up in this study limits conclusions about <sup>68</sup>Ga-DOTATATE PET CT's potential effect on survival. Finally, no guidelines exist recommending a treatment sequence for metastatic NET; therefore, some treatment decisions may vary by clinicians and center, which would influence the percentage of patients undergoing a change in management after <sup>68</sup>Ga-DOTATATE PET CT. The aim of this study was not to determine whether certain treatment options should be applied instead of or before others, but rather to describe changes in management as they occurred after <sup>68</sup>Ga DOTATATE PET CT was performed in a single institution.

Despite these limitations, we found that in our center, <sup>68</sup>Ga-DOTATATE PET CT was associated with a change in treatment management in the majority of patients with NETs. Further research should focus on determining optimal timing of <sup>68</sup>Ga-DOTATATE PET CT usage in NET patients.

### Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

### References

- Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121:589–597.
- Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology*. 2016;103:172–185.
- Tirosh A, Kebebew E. The utility of <sup>68</sup>Ga-DOTATATE positron-emission tomography/computed tomography in the diagnosis, management, follow-up and prognosis of neuroendocrine tumors. *Future Oncol Lond Engl*. 2018;14:111–122.
- Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (<sup>68</sup>Ga)-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging*. 2014;4:426–434.
- Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using <sup>68</sup>Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and <sup>18</sup>F-FDG. *Cancer*. 2008;112:2447–2455.
- Barrio M, Czernin J, Fanti S, Ambrosini V, Binse I, Du L, et al. The impact of somatostatin receptor-directed PET/CT on the management of patients with neuroendocrine tumor: a systematic review and meta-analysis. *J Nucl Med Off Publ Soc Nucl Med*. 2017;58:756–761.
- Deppen SA, Liu E, Blume JD, Clanton J, Shi C, Jones-Jackson LB, et al. Safety and efficacy of <sup>68</sup>Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. *J Nucl Med Off Publ Soc Nucl Med*. 2016;57:708–714.
- Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of <sup>68</sup>Ga-DOTATATE. *J Nucl Med Off Publ Soc Nucl Med*. 2013;54:855–860.
- Sadowski SM, Neychev V, Millo C, Shih J, Nilubol N, Herscovitch P, et al. Prospective study of <sup>68</sup>Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol Off J Am Soc Clin Oncol*. 2016;34:588–596.
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Neuroendocrine Tumors Version 3.2017 [Internet]. National Comprehensive Cancer Network; 2017. Available from: [https://www.nccn.org/professionals/physician\\_gls/pdf/neuroendocrine.pdf](https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf). Accessed: October 15, 2017.
- R Core Team. Vienna, Austria: R Foundation for Statistical Computing; 2016. Available from: <https://www.R-project.org/>. Accessed: October 15, 2017.
- Skoura E, Michopoulou S, Mohmaduvash M, Panagiotidis E, Al Harbi M, Toumpanakis C, et al. The impact of <sup>68</sup>Ga-DOTATATE PET/CT imaging on management of patients with neuroendocrine tumors: experience from a national referral center in the United Kingdom. *J Nucl Med Off Publ Soc Nucl Med*. 2016;57:34–40.
- Nockel P, Millo C, Keutgen X, Klubo-Gwiezdzińska J, Shell J, Patel D, et al. The rate and clinical significance of incidental thyroid uptake as detected by Gallium-68 DOTATATE positron emission tomography/computed tomography. *Thyroid Off J Am Thyroid Assoc*. 2016;26:831–835.
- Kuyumcu S, Özkan ZG, Sanli Y, Yilmaz E, Mudun A, Adalet I, et al. Physiological and tumoral uptake of <sup>68</sup>Ga-DOTATATE: standardized uptake values and challenges in interpretation. *Ann Nucl Med*. 2013;27:538–545.
- Haug AR, Cindea-Drimus R, Auernhammer CJ, Reincke M, Wängler B, Uebleis C, et al. The role of <sup>68</sup>Ga-DOTATATE PET/CT in suspected neuroendocrine tumors. *J Nucl Med Off Publ Soc Nucl Med*. 2012;53:1686–1692.
- Janssen I, Chen CC, Millo CM, Ling A, Taieb D, Lin FI, et al. PET/CT comparing (<sup>68</sup>Ga)-DOTATATE and other radiopharmaceuticals and in comparison with CT/MRI for the localization of sporadic metastatic pheochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging*. 2016;43:1784–1791.
- Janssen I, Blanchet EM, Adams K, Chen CC, Millo CM, Herscovitch P, et al. Superiority of [<sup>68</sup>Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2015;21:3888–3895.
- Chang CA, Pattison DA, Tothill RW, Kong G, Akhurst TJ, Hicks RJ, et al. (<sup>68</sup>Ga)-DOTATATE and (<sup>18</sup>F)-FDG PET/CT in paraganglioma and pheochromocytoma: utility, patterns and heterogeneity. *Cancer Imaging Off Publ Int Cancer Imaging Soc*. 2016;16:22.
- Hope TA, Bergsland EK, Bozkurt MF, Graham M, Heaney AP, Herrmann K, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. *J Nucl Med*. 2018;59:66–74.
- Haug AR, Cindea-Drimus R, Auernhammer CJ, Reincke M, Beuschlein F, Wängler B, et al. Neuroendocrine tumor recurrence: diagnosis with <sup>68</sup>Ga-DOTATATE PET/CT. *Radiology*. 2014;270:517–525.

## Discussion

**Dr Chee-Chee Stucky** (Scottsdale, AZ): That was a very nice presentation and really interesting. My question for you regards the patients had biochemical concern for a neuroendocrine tumor but the DOTATATE was negative. Are you now not using follow-up biochemical markers for your surveillance as you feel that the DOTATATE is more sensitive?

**Dr Xavier Keutgen:** I think we all see a lot of patients that have disease but don't have a real positive biochemical profile. What you most commonly follow is chromogranin A, and chromogranin A has been shown to have a lot of false positives. But I wouldn't say that one shouldn't use it anymore. I still use it.

I would say it does help me sometimes to use the DOTATATE scan for surveillance. Typically, the insurance company will only pay for it once per year. So if I have a patient with a history of a neuroendocrine tumor with high preoperative chromogranin A levels that normalized after surgery, but then increased again without an obvious source on the CT scan, that's the time that I would use the DOTATATE.

So I still do think that there's some value in using chromogranin A as a marker. But I would say that it's probably helpful in just a minority of patients.

**Dr James Howe** (Iowa City, IA): Xavier, great job of getting DOTATATE up and running at your institution and carefully reviewing your results so we can all learn from you.

The sensitivity of these scans is so high that a lot of our patients have widespread bony metastases that we never realized, or they may have extrahepatic disease.

My question is whether you use the presence of bony metastases to keep you from doing cytoreductive liver surgery?

A second question is about false positives. I was curious about how many false positives you had in your group, and what you do about possible false positives in the uncinate process of the pancreas? How do you do further workup when you see uptake in the head of the pancreas?

**Dr Xavier Keutgen:** I would say that extrahepatic disease should not be an actual contraindication to perform cytoreductive liver surgery. We know that 80% of these patients die of liver metastases; they don't die of bone metastases. There is a risk that now that DOTATATE is in more widespread use that oncologists will potentially not refer these patients to us because they see that they have extrahepatic disease.



I will refer to Dr Chen's poster, in which we analyzed over 60,000 stage IV patients in the NCDB database. We specifically looked at those that had debulking surgery with only liver metastases and those with extrahepatic metastases. We found that even though their survival with extrahepatic metastasis was not as good as liver-only, it was still vastly better than no surgery.

The fact is that we don't have any good systemic therapies to treat their liver disease so I would not say to a patient that has extrahepatic disease that we shouldn't debulk them.

Regarding the uncinate process of the pancreas, we know that that's a common false positive location. I think it depends a little bit on your radiologist and how experienced they are in reading those scans. Initially, I connected our radiologist with a radiologist at the National Institutes of Health in order to try and understand what represents a false positive and what does not.

So in regards to the uncinate process, if they have a primary tumor somewhere else and I know where it is, I would not work it up further if my radiologist tells me they have little suspicion. If it's an unknown primary, then maybe.

**Dr Janice Pasiaka** (Calgary, AB): Xavier, thank you very much. Just to follow up on what James is saying, what percentage of your cohort had unsuspected bony metastases or disease outside of the abdominal cavity? What is the number we are going to be looking at?

**Dr Xavier Keutgen:** I don't know that number right now, but I would guess it's probably around 20%.

**Dr Rodney Pommier** (Portland, OR):

My question has to do with the patients who had no biopsy-proven tumor. Every time I am asked to speak at a large patient conference, there are many that come up to me afterwards and say that they know we find these difficult primaries 90% of the time and ask me to operate because nobody has found their tumor. I have to point out to them that I found these primaries in people that had incontrovertible biochemical proof that they had one. The fact that a surgeon couldn't find it only reinforces the patient's belief that they must have a neuroendocrine tumor.

I have gotten calls from medical examiners because people have actually died during angiography being done to hunt for these tumors. I send them a bunch of pictures of neuroendocrine tumors, and none of these patients had anything found at their very thorough autopsies either.

So did the negative Gallium DOTATATE scans stop their pursuit? Did it convince them that they don't have a tumor?

**Dr Xavier Keutgen:** That's a great question. It applies to perhaps 5 or 6 patients in the study for whom we did a Gallium DOTATATE. It was actually for suspicion of pheochromocytoma. It's not the traditional population that you think of. So for those patients, I would say that if you have a negative scan (in the setting of 2- to 4-fold elevation of metanephrines) you likely do not have a tumor.

In terms of all the other NET patients, I agree with you. DOTATATE is good, but it's not as good as having your hands in the abdomen and feeling it. Sometimes the tumors are so small you can't see them. I know very well about your series. So I do not think that a negative DOTATATE should stop you from doing an operation or from trying to find the tumors 1 way or another.