Published in final edited form as:

J Am Coll Surg. 2015 August ; 221(2): 509–517. doi:10.1016/j.jamcollsurg.2015.04.005.

⁶⁸Gallium-DOTATATE PET/CT Scanning Results in Patients with MEN1

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Abstract

Background—Screening for neuroendocrine tumors (NETs) in patients with multiple endocrine neoplasia type 1 (MEN1) is recommended to detect primary and metastatic tumors, which can result in significant morbidity and mortality. The utility of somatostatin receptor imaging ⁶⁸Gallium-DOTATATE PET/CT in patients with MEN1 is not known. The aim of this study was to prospectively determine the accuracy of ⁶⁸Gallium-DOTATATE PET/CT versus ¹¹¹In-pentetreotide SPECT/CT and anatomic imaging in patients with MEN1.

Study design—Prospective study comparing ⁶⁸Gallium-DOTATATE PET/CT, ¹¹¹In-pentetreotide SPECT/CT, and triphasic CT scan to clinical, biochemical and pathological data in 26 patients with MEN1.

Results—⁶⁸Gallium-DOTATATE PET/CT detected 107 lesions; ¹¹¹In-pentetreotide SPECT/CT detected 33 lesions; and CT scan detected 48 lesions. Lesions detected on ⁶⁸Gallium-DOTATATE PET/CT had high SUV_{max} (median SUV_{max} = 72.8 [range 19–191]). In 7 of the 26 patients (27%), ⁶⁸Gallium-DOTATATE PET/CT was positive with a negative ¹¹¹In-pentetreotide SPECT/CT, and in 10 patients (38.5%), additional metastases were detected (range 0.3 cm to 1.5

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Disclosure Information: Nothing to disclose.

Presented at the World MEN meeting, Vienna, Austria, September 2014.

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cm). In 8 of the 26 patients (31%), there was a change in management recommendations as a result of the findings on ^{68}Ga -DOTATATE PET/CT that were not seen on ^{111}In -pentetreotide SPECT/CT and CT scan.

Conclusions— ^{68}Ga -DOTATATE PET/CT is more sensitive for detecting NETs than ^{111}In -pentetreotide SPECT/CT and CT scan in patients with MEN1. This imaging technique should be integrated into radiologic screening and surveillance of patients with MEN1, as it can significantly alter management recommendations.

Multiple endocrine neoplasia type 1 (MEN1) is one of the most common familial cancer syndromes. MEN1 is an autosomal dominant hereditary syndrome caused by a germline mutation in the *MEN1* tumor suppressor gene. It has a prevalence of 2 to 3 per 100,000.¹ MEN1 is characterized by the occurrence of tumors in the parathyroid glands and neuroendocrine tumors (NETs) in the pancreatic islets and gastrointestinal tract, the anterior pituitary, and less commonly in the thymus, lung, bronchus, and the adrenal cortex.

Although the most common manifestation of MEN1 is the development of primary hyperparathyroidism as a result of parathyroid tumors hypersecreting parathyroid hormone, most morbidity and mortality in patients with MEN1 results from NETs involving the gastrointestinal tract, pancreatic islets, bronchus, and thymus, which have high penetrance and malignant potential.²⁻⁴ Thus, once a diagnosis of MEN1 is established in an individual based on clinical manifestations and/or genetic testing results, an active surveillance program is instituted for early detection and treatment of MEN1-associated disease, especially for tumor sites with malignant potential, such as gastrointestinal and pancreatic NETs.⁵ Clinical practice guidelines have been developed for surveillance and screening for MEN1-associated tumors and include clinical, biochemical, and imaging studies, which often depend on local expertise and resources that are available at each institution.⁵ However, there are limited data on the most accurate methods for screening patients with MEN1 for gastrointestinal and pancreatic NETs, which account for a significant proportion of MEN1-related morbidity and mortality.²

Positron emitting radiopharmaceuticals for somatostatin receptor imaging, DOTA analogs, have been developed and subsequently evaluated in patients with NETs and show promising results, with high accuracy in detecting primary, recurrent, and metastatic tumors as compared to anatomic imaging, traditional radiopharmaceuticals, and endoscopy for gastrointestinal and pancreatic NETs. These radioligands, which include ^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC, and ^{68}Ga -DOTANOC, have a high affinity to somatostatin receptors, especially to type 2 (SSTR 2). A comparison of this new somatostatin receptor imaging in a meta-analysis of retrospective studies suggested that ^{68}Ga -DOTATATE was most accurate for detecting NETs, with pooled sensitivities of 96% and 93%, and pooled specificities of 100% and 85%, respectively, when comparing ^{68}Ga -DOTATATE to ^{68}Ga -DOTATOC.⁶ In the United States, many of these new radioligands are investigational for the detection of NETs. Moreover, the clinical utility of ^{68}Ga -DOTATATE for screening and or surveillance in patients with MEN1 is unknown.

In this study, we prospectively compared the accuracy of ^{68}Ga -DOTATATE positron emission tomography/computed tomography (PET/CT), ^{111}In -pentetreotide single-photon emission computed tomography (SPECT/CT) and anatomic imaging with CT scan in addition to clinical and biochemical screening in patients with MEN1.

Methods

The diagnosis of MEN1 was made based on 1) the presence of primary hyperparathyroidism combined with anterior pituitary tumor and/or gastrointestinal and pancreatic neuroendocrine tumor; 2) a diagnosis of primary hyperparathyroidism combined with a diagnosis of MEN1 in at least one first-degree relative; or 3) a positive germline mutation in the *MEN1* gene. All patients underwent screening and surveillance tests for other manifestations of MEN1, per published guidelines.⁷

Clinical and biochemical evaluation in patients with MEN1

Patients with MEN1 have yearly follow-up at the National Institutes of Health (NIH) Clinical Center, which includes laboratory and imaging evaluations, as well as an endoscopy (esophagus, stomach and duodenum) and gastric pH measurement to screen for primary hyperparathyroidism, kidney stones by kidney ultrasound, Zollinger-Ellison Syndrome, gastric and duodenal ulcers, bone density by dual energy X-ray absorptiometry, pituitary tumors, pancreatic and gastrointestinal NETs. Personalized treatment and management is performed according to results of these screening tests. Our screening and follow-up laboratory studies included measurement of chromogranin A, pancreatic polypeptide, neuron-specific enolase, vasoactive intestinal polypeptide, urinary 5-hydroxyindoleacetic acid (5-HIAA), fasting gastrin, somatostatin, catecholamines and metanephrines, calcitonin, fasting insulin, C-peptide (proinsulin) and glucagon.

Imaging evaluation in patients with MEN1

^{68}Ga -DOTATATE PET/CT is considered investigational in the United States and is not approved for routine use to localize NETs; therefore, the current study was performed under a research protocol approved by the National Cancer Institute Review Board and the NIH Radiation Safety Committee (NCT01967537) under an Investigational New Drug approval from the U.S. Food and Drug Administration. Through a peripheral vein, 5 mCi of ^{68}Ga -DOTATATE was administered. After approximately 60 min, the patient was positioned supine in a PET/CT scanner (Siemens Medical Solutions USA, Inc.), and images from the upper thighs to mid-skull (including pituitary gland) were obtained. A low-dose, non-contrast CT was used for attenuation correction and anatomic localization. Maximum standardized uptake values (SUV_{max}) were measured based on patient total body weight.

An ^{111}In -pentetreotide SPECT/CT with imaging at 4 h and at 24 h following intravenous administration of 6 mCi (222 MBq) of ^{111}In -pentetreotide was performed within 4 weeks of ^{68}Ga -DOTATATE PET/CT, to allow for direct comparison. Further anatomic imaging, including chest, abdominal, and pelvic CT scan was performed in all subjects using LightSpeed Ultra, LightSpeed QX/i (General Electric Healthcare Technologies, Waukesha, WI), and Mx8000 IDT (Philips Medical Systems, Andover, MA) scanners (arterial and

portal venous phase, 2 mm slices, with a rapid infusion of nonionic water-soluble contrast agent [130 mL injected at 2 mL/s], as well as oral contrast) within 4 weeks from ^{68}Ga -DOTATATE PET/CT scanning. Anatomical imaging of the brain was performed when clinically indicated based on results from PET or SPECT/CT.

Images were reviewed by independent radiologists and nuclear medicine physician in a blinded fashion. Further, all imaging studies were analyzed and correlated with clinical information by a multidisciplinary team to determine the optimal treatment options based on the functional status of the NETs, risk of malignancy based on tumor size for nonfunctioning pancreatic NET, and/or the presence of metastatic disease. Change in management was defined as a change in surveillance or treatment strategies that occurred as a result of the findings on ^{68}Ga -DOTATATE PET/CT as compared to the findings on CT/MRI and ^{111}In -pentetreotide SPECT/CT.

Statistical Analyses

Statistical analyses were performed using GraphPad Prism 5 software (GraphPad Software, La Jolla, CA). Data were analyzed using Pearson and Spearman correlation tests. Two-tailed $P < 0.05$ was considered statistically significant. Data are presented as mean $\pm$ standard deviation (SD) or median (range).

Results

Study cohort and imaging results

The study cohort demographics, clinical characteristics and biochemical profiles are summarized in Table 1. A total of 26 patients with a known diagnosis of MEN1 were enrolled, with a mean age of 42 ± 15 years. Of these 26 patients, 14 had prior history of histologically proven NET (7 nonfunctioning pancreatic NETs [PNETs]; 3 insulinoma; 3 gastrinoma; 1 thymic carcinoid). The median chromogranin A level was 284 (range 23–18,710; normal <93 ng/mL), the median fasting gastrin level was 194 (range 10–17,290; normal <100 pg/mL), and the median pancreatic polypeptide was 225 (range 61–2500; normal <291 pg/mL).

As shown in Table 2, 107 lesions were detected by ^{68}Ga -DOTATATE PET/CT, 33 lesions were detected by ^{111}In -pentetreotide SPECT/CT, and 48 lesions were detected by triphasic CT scan. All lesions detected on ^{111}In -pentetreotide SPECT/CT and triphasic CT were also detected on ^{68}Ga -DOTATATE PET/CT (Table 2). In 7 patients, ^{111}In -pentetreotide SPECT/CT was negative, but ^{68}Ga -DOTATATE PET/CT found lesions with uptake: 7 pancreatic lesions and 1 duodenal lesion were identified.

The median SUV_{max} of ^{68}Ga -DOTATATE avid lesions was 73 (range 19–191). The sites of disease detected by ^{68}Ga -DOTATATE PET/CT, in addition to those found on ^{111}In -pentetreotide SPECT/CT and triphasic CT, included pancreatic head, body, and tail primary tumors; duodenal and gastric primary tumors; and metastatic sites of disease in the liver; retroperitoneal, peripancreatic, and mesenteric lymph nodes; and primary tumors in the appendix and lung. There was no correlation between the serum levels of chromogranin A, gastrin, and the number of lesions detected or SUV_{max} on ^{68}Ga -DOTATATE.

However, the pancreatic polypeptide serum levels correlated significantly with the number of lesions on ^{68}Ga -DOTATATE PET/CT (Spearman $r = 0.72$, $P < 0.005$; $N = 15$).

A representative case of lesions detected with the three modalities is shown in Figure 1. In this case, a 60-year-old man with MEN1 was found to have metastatic gastrinoma (Case #2, Table 3) with ^{68}Ga -DOTATATE PET/CT showing a lung lesion and multiple duodenal gastrinomas with metastases to the lymph nodes (red arrows, Figure 1C). Not all lesions were identified on the initial blinded reading of the CT scan (red arrows, Figure 1D), and ^{111}In -pentetreotide SPECT showed only a lung lesion. In Figure 2, we show an example of an 81-year-old woman with MEN1 and known liver metastases. ^{68}Ga -DOTATATE PET/CT showed a much higher tumor burden than that found with ^{111}In -pentetreotide SPECT and CT scan (Figure 2).

Management recommendations

Given the higher number of lesions detected on ^{68}Ga -DOTATATE PET/CT, we analyzed how these findings altered the management of patients with MEN1 undergoing surveillance imaging annually in our clinical protocol. After clinically evaluating patients and analyzing all imaging results, which were read prior to knowledge of the findings on other imaging studies, the optimal treatment options were considered based on the functional status of the NETs, risk of malignancy, and/or the presence of metastatic disease. In 10 patients (38.5%), ^{68}Ga -DOTATATE PET/CT detected new metastatic lesions, which were not seen on ^{111}In -pentetreotide SPECT/CT; in 7 of these, ^{68}Ga -DOTATATE PET/CT detected retroperitoneal lymph nodes (smallest in size: 0.7cm), and in 1 of them, an additional mesenteric lymph node; in 4 of these patients, these lymph node metastases were not seen on CT scan; in 1 patient, ^{68}Ga -DOTATATE PET/CT detected a small, 0.3 cm lung nodule (positive on CT as well); in 1 patient, a lesion in the appendix was found (not seen on CT), and in another patient multiple additional liver lesions were found. In 11 patients, ^{68}Ga -DOTATATE PET/CT found more lesions than were found with ^{111}In -pentetreotide SPECT/CT, without leading to a change in management. Three patients were followed by surveillance more frequent than once a year, as no baseline with ^{68}Ga -DOTATATE PET/CT was available to determine whether their metastatic disease had progressed significantly enough to recommend therapy.

Overall, there was a change in management in 8 of the 26 patients (31%). In 7 patients, surgical resection of the primary or metastatic disease was recommended based on risk of malignancy or metastases from a primary tumor, and in 1 patient, systemic therapy (sunitinib) was recommended for progressive metastatic NETs. Summarized in Table 3 are the results of those patients who underwent surgical resection after performing ^{68}Ga -DOTATATE PET/CT, with correlation between imaging study results and histologic findings. Three of the patients in Table 3 had undergone previous distal pancreatectomy (Cases #2, 5 and 6).

In 5 of 7 patients (71.4%) with histopathologic confirmation, the additional lesions found on ^{68}Ga -DOTATATE PET/CT was confirmed to be positive. In 4 patients histopathology confirmed metastatic lymph-nodes, and in 1 case ^{68}Ga -DOTATATE PET/CT detected an NET of the appendix. In 2 of the 7 patients who had an operation (case

#3 and 4), the additionally suspected lymph nodes on ^{68}Ga -DOTATATE PET/CT were not confirmed by histopathology, but both required removal of their primary tumor due to the risk of malignancy (large primary tumor size) and case #3 had a grade 2 primary tumor. A per-lesion analysis in patients who had an operation showed all primary tumors and 23 of 28 lymph nodes were true positive by histology.

Discussion

In this study, we investigated the clinical utility of ^{68}Ga -DOTATATE PET/CT scanning in patients with MEN1 who are considered a high-risk population for NETs. In comparison to currently used screening and surveillance imaging studies for NETs in patients with MEN1, ^{68}Ga -DOTATATE was superior to ^{111}In - pentetreotide SPECT/CT and anatomical imaging in the detection of primary as well as metastatic NETs. As a result of ^{68}Ga -DOTATATE PET/CT findings, patient management recommendations were altered in 31% of patients because of the risk of a primary malignant NETs or the detection of metastatic NETs not initially found.

The current standard functional imaging technique for NETs is octreotide scintigraphy, targeting the SSTR 2, but with variable diagnostic sensitivity of 65% to 100% according to tumor site of origin.^{8,9} PET with ^{68}Ga -labeled somatostatin ligands has been used as a tool in localizing unknown primary tumors in metastatic NETs.^{10,11} The use of PET/CT with ^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC, or ^{68}Ga -DOTANOC has been demonstrated as a clinically effective technique for the evaluation of patients with NETs. These tracers have high affinity for SSTR 2, but can also bind with varying affinity to the other SSTR subtypes. The in vitro affinity of ^{68}Ga -DOTATATE in binding SSTR 2 is approximately 10-fold higher than that of ^{68}Ga -DOTATOC.¹² Because this receptor subtype is predominantly overexpressed in NETs, this difference may be of clinical relevance. Hofman and colleagues¹³ reported that ^{68}Ga -PET was more effective than ^{111}In - pentetreotide SPECT/CT and conventional imaging (CT, magnetic resonance imaging [MRI], bone scintigraphy) in the identifying additional sites of disease, with bone and local lymph nodes being the most frequent sites of disease detected. Several investigators have also shown that ^{68}Ga -labeled somatostatin PET was more effective than FDG PET and FDOPA PET in detecting NETs.¹⁴⁻¹⁶ Frilling and associates¹⁷ showed ^{68}Ga -PET/CT was more accurate than CT and/or MRI in detecting additional hepatic and/or extrahepatic metastases. Thus, the European Neuroendocrine Tumor Society has recommended use of ^{68}Ga -labeled somatostatin receptor PET as a diagnostic modality for patients with NETs.¹⁸ The use of this modality is recommended for staging, and its use could lead to changes in management strategies.^{13,17} It has also been shown to be a useful imaging tool in detecting early recurrences after resection of NET,¹⁹ which is important in the treatment of patients with MEN1. Furthermore, ^{68}Ga -DOTATATE PET/CT scanning may have several other advantages over ^{111}In - pentetreotide SPECT/CT and abdominal CT scan. It requires a shorter imaging time and has a lower cost than ^{111}In - pentetreotide SPECT/CT.²⁰ ^{68}Ga -DOTATATE PET has a lower radiation exposure (1.1 rem) than ^{111}In -pentetreotide SPECT/CT (1.6 rem) and abdominal CT scanning (2.5 rem).²¹ ^{68}Ga -DOTATATE is generator-produced and thus does not require a cyclotron, allowing for a lower cost and wider usage.

In our study, because not all patients underwent surgery for removal of all imaged-based suspected lesions, it is impossible to reach definitive conclusions regarding the accuracy of the positive findings. In 5 of 7 patients who had surgery, all ^{68}Ga -DOTATATE findings were positive on histologic examination, and the smallest lesion detected by ^{68}Ga -DOTATATE was 0.8 cm; this includes two cases in which pathology showed additional positive lymph nodes, suggesting that ^{68}Ga -DOTATATE PET/CT detects low volume of disease. However, in 2 patients, not all of the lymph nodes seen on ^{68}Ga -DOTATATE were positive on histologic examination. In a per-lesion analysis, 23 lesions were true positive and 5 lesions were false positive based on histologic examination. This may be due to several reasons. The lymph node involved was not in the surgical specimen removed or it was a false positive result on ^{68}Ga -DOTATATE. In both cases it was the risk that the primary tumor may be malignant (based on tumor size) that the patients were recommended to have an operation. False positive ^{68}Ga -DOTATATE result may be due to indeterminate uptake (SUV less than 10) from SSTR2 positive macrophages in lymph-nodes as has been shown in inflammatory cardiovascular disease.^{22, 23} However, the positive lymph nodes in our cases had high SUV_{max} (21 and 34, respectively). Nonetheless ^{68}Ga -DOTATATE PET/CT was helpful in clarifying the diagnosis of a primary PNET in both cases. In patients who did not have the gold standard of diagnosis by histologic examination, 18 patients had additional lesions detected by ^{68}Ga -DOTATATE. While we cannot be certain these don't represent false positive results, these additional lesions were found in the liver (17), peripancreatic lymph nodes (9), and duodenum (12) in patients with biochemical evidence of gastrinoma, as well as in the stomach (1), pancreas (31), appendix (1), and lung (1). Furthermore, in 13 of 16 patients with additional lesions detected by ^{68}Ga -DOTATATE that were not detected by CT or ^{111}In -pentetreotide SPECT/CT, the chromogranin A and/or pancreatic polypeptide serum levels were elevated.

To our knowledge, the current study is the first prospective study of ^{68}Ga -DOTATATE PET/CT in patients with MEN1. As previously mentioned, most morbidity and mortality in patients with MEN1 result from gastrointestinal, thymic and pancreatic NETs.²⁻⁴ Thus, once a diagnosis of MEN1 is established in an individual based on clinical manifestations and/or genetic testing results, an active surveillance program is instituted for early detection and treatment of MEN1-associated disease, especially for tumor sites with malignant potential, such as gastrointestinal and pancreatic NETs.⁵ Such an approach can lead to early detection of NETs and treatment to reduce morbidity and mortality in these patients.

Our study has some limitations. We do not have long-term follow-up data on patients who had ^{68}Ga -DOTATATE-avid lesions to determine whether the amount of avidity correlates with disease progression. We also do not have the gold standard diagnosis (histopathology) for every lesion detected to determine its overall accuracy. Lastly, while the results of ^{68}Ga -DOTATATE significantly altered the management recommendations in some of the patients with MEN1, the study design (not a randomized controlled trial) does not allow us to know definitively whether if this change in management results in improved long-term patient outcome.

In conclusion, in patients with MEN1, ⁶⁸Gallium-DOTATATE PET/CT is more sensitive for detecting NETs than ¹¹¹In- pentetreotide SPECT/CT and CT scan. This technique should be integrated into radiologic screening of patients with MEN1 as it can significantly alter management recommendations. Future studies that include a longer follow-up time and a larger cohort of patients who have familial cancer syndromes and are at risk for developing NETs will shed light on whether patient morbidity and mortality would be impacted.

Acknowledgments

Support: This research was supported by the intramural research programs of the Center for Cancer Research, National Cancer Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

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Abbreviations and Acronyms

CT	computer tomography
5-HIAA	5-hydroxyindoleacetic acid
MEN1	multiple endocrine neoplasia type 1
MIP	maximum intensity projection
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
NIH	National Institutes of Health
PET	positron emission tomography

SSTR 2	somatostatin receptor type 2
SPECT	single-photon emission computerized tomography
SUV	standard uptake value
WHO	World Health Organization

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Figure 1.

A 60-year-old man with MEN1 and metastatic gastrinoma found on ^{68}Ga -DOTATATE PET/CT (pt. no. 2 in Table 3) where (A) ^{111}In -pentetreotide scan (planar) shows a left lung lesion, (B) ^{68}Ga -DOTATATE PET maximum intensity projection (MIP) image shows left lung lesion and multiple lesions in the abdomen, (C) ^{68}Ga -DOTATATE PET/CT resolves the abdominal lesions as localizing within the duodenum (gastrinomas) and lymph nodes (metastatic) (arrows), and (D) arterial phase CT with duodenal gastrinoma (white arrow) and metastatic lymph node (red arrow). MEN1, Multiple Endocrine Neoplasia Type 1

Figure 2.

An 81-year-old woman with MEN1 and known liver metastases where (A) ^{111}In -pentetreotide scan (planar) shows abnormal liver uptake, (B) ^{68}Ga -DOTATATE PET MIP image shows innumerable (> 20) liver metastases, (C) ^{68}Ga -DOTATATE PET/CT image show multiple liver lesions (arrows), (D) arterial phase CT show corresponding hypodense liver lesions (arrows), and (E) venous phase CT show corresponding hypodense liver lesions (arrows). MEN1, Multiple Endocrine Neoplasia Type 1.

Table 1
Clinical and Biochemical Profile of MEN1 Study Cohort

Variable	Patients with MEN1, n = 26
Sex, n	
Male	17
Female	9
Age, y, mean $\pm$ SD [range]	42 $\pm$ 15 [19–82]
Patients with manifestations of MEN1*, n	
Primary hyperparathyroidism	18
Pituitary tumors	12
Zollinger-Ellison syndrome	11
Adrenocortical adenoma	1
Thymic carcinoid	1
Angiofibroma	3
Fasting chromogranin A, median [range, normal <93 ng/mL]	284 [23–18710]
Fasting gastrin, median [range, normal <100 pg/mL]	194 [10–17290]
Fasting neuron specific enolase, median [range, normal <15 ng/mL]	9.9 [6.2–13]
Fasting pancreatic polypeptide, median [range, normal <291 pg/mL]	225 [61–2500]
Urinary 5 HIAA, median [range, normal <8mg/24h]	4.85 [1.9–9.4]
SUV _{max} on ⁶⁸ Ga-DOTATATE PET/CT, median [range]	72.8 [19.2–191]
Patients with a history of histologically proven NET, n (%)	14 (54)
Type of NETs, n	
Nonfunctioning pancreatic	7
Insulinoma	3
Gastrinoma	3
Thymic carcinoid	1
Patients with prior abdominal surgery, n (%)	10 (39)
Patients in which surgery was recommended [†] , n (%)	7 (27)
Patients in which systemic therapy was recommended [†] , n (%)	1 (4)

* Some patients had more than one manifestation.

[†] based on ⁶⁸Ga-DOTATATE PET/CT.

MEN1, multiple endocrine neoplasia type 1; SD, standard deviation.

Table 2

Concordance of Imaging Study Results per Lesion Analysis.

	CT	¹¹¹ In-pentetreotide	DOTATATE
CT, n	48	19	48
¹¹¹ In- pentetreotide, n	-	33*	32
DOTATATE, n	-	-	107

* Liver lesion seen on ¹¹¹In- pentetreotide was negative on ⁶⁸Ga-DOTATATE PET/CT, MRI, and arterial phase CT and was thus considered an artifact of ¹¹¹In- pentetreotide SPECT/CT.

Table 3
Correlation of Imaging Results with Pathology in 7 Patients with MEN1 Who Underwent Surgery

Patient No.	Diagnoses	Imaging study, no. of lesions	Operation	Pathology
1	MEN1, heterogenous pancreatic head mass	⁶⁸ Ga-DOTATATE (2 PNET, 2 retropancreatic LN), 4; ¹¹¹ In-pentetreotide (2 PNET), 2; CT, 1	Whipple procedure, DP, LN resection	Multiple metastatic NET, WHO 2, pT3 pN1 (1/8)
2	MEN1, gastrinoma with LN metastases	⁶⁸ Ga-DOTATATE (4 DD, LN, lung), 8; ¹¹¹ In-pentetreotide (lung), 1; CT (3 DD, 1 lung), 4	Duodenotomy, LN resection	Gastrinoma, WHO1, pT2 N1 (13/24)
3	MEN1, PNET with celiac LN	⁶⁸ Ga-DOTATATE (PNET, lung, LN), 3; ¹¹¹ In-pentetreotide (lung), 1; CT (PNET, lung, LN), 3	Pancreatic EN, LN resection	PNET, WHO 2, pT2 N0 (0/3)
4	MEN1, PNET with retropancreatic LN	⁶⁸ Ga-DOTATATE (2 PNET, 2 LN), 4; ¹¹¹ In-pentetreotide (1 PNET), 1; CT (2 PNET), 2	Pancreatic tail EN, LN resection	PNET, 9 cm, WHO 1, pT2 N0 (0/10)
5	MEN1, PNET metastatic to LN	⁶⁸ Ga-DOTATATE (1 PNET, 3 LN), 4; ¹¹¹ In-pentetreotide (1 PNET, 2 LN), 3; CT (1 PNET, 2 DD gastrinoma), 3	Periportal/retropancreatic/LN resection	Metastatic NET to LN, WHO 1
6	MEN1, PNET with retroperitoneal LNs and uterine mass	⁶⁸ Ga-DOTATATE (1 PNET, 2 DD, 3 LN, 1 uterus), 7; ¹¹¹ In-pentetreotide (1 DD, 2 LN, 1 uterus), 4; CT (1 PNET, 1 DD, 2 LN, 1 uterus), 5	Pancreatic EN, duodenotomy, peripancreatic and periaortic LN resection, salphingo-oophorectomy	PNET WHO 1, gastrinomas, peripancreatic and periaortic LN 10/11; uterus: NEC, pT3, N1 (4/7)
7	MEN1, PNET and appendiceal lesion	⁶⁸ Ga-DOTATATE (3 PNET, 1 appendix), 4; ¹¹¹ In-pentetreotide, 0; CT (1 PNET), 1	Appendectomy	NET of appendix, 0.7 cm at tip, WHO 1

MEN1, multiple endocrine neoplasia type 1; DP, distal pancreatectomy; EN, enucleation; LN, lymph node; DD, duodenum; PNET, pancreatic NET; TNM stage according to the American Joint Committee on Cancer^{24, 25} and the World Health Organization histologic classification for PNET (1 low grade NET; 2 intermediate NET; 3 high-grade NEC).²⁶