Results of ^{68}Gallium-DOTATATE PET/CT Scanning in Patients with Multiple Endocrine Neoplasia Type 1

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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 ^{68}Gallium-DOTATATE PET/CT in patients with MEN1 is not known. The aim of this study was to prospectively determine the accuracy of ^{68}Gallium-DOTATATE PET/CT vs ^{111}In- pentetreotide single-photon emission CT (SPECT)/CT and anatomic imaging in patients with MEN1.

STUDY DESIGN: We performed a prospective study comparing ^{68}Gallium-DOTATATE PET/CT, ^{111}In-pentetreotide SPECT/CT, and triphasic CT scan to clinical, biochemical, and pathologic data in 26 patients with MEN1.

RESULTS: ^{68}Gallium-DOTATATE PET/CT detected 107 lesions; ^{111}In-pentetreotide SPECT/CT detected 33 lesions; and CT scan detected 48 lesions. Lesions detected on ^{68}Gallium-DOTATATE PET/CT had high standard uptake value $(SUV)_{max}$ (median $SUV_{max} = 72.8$ [range 19 to 191]). In 7 of the 26 patients (27%), ^{68}Gallium-DOTATATE PET/CT was positive, with a negative ^{111}In-pentetreotide SPECT/CT, and in 10 patients (38.5%), additional metastases were detected (range 0.3 cm to 1.5 cm). In 8 of the 26 patients (31%), there was a change in management recommendations as a result of the findings on ^{68}Gallium-DOTATATE PET/CT that were not seen on ^{111}In-pentetreotide SPECT/CT and CT scan.

CONCLUSIONS: ^{68}Gallium-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 because it can significantly alter management recommendations. (J Am Coll Surg 2015;221:509–517. © 2015 by the American College of Surgeons)

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Multiple endocrine neoplasia type 1 (MEN1) is one of the most common familial cancer syndromes. It 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] and 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 development of primary hyperparathyroidism as a result of parathyroid tumors hypersecreting parathyroid hormone, most morbidity and mortality in patients with MEN1 result from NETs involving the gastrointestinal tract,

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Abbreviations and Acronyms

MEN1 = multiple endocrine neoplasia type 1
NET = neuroendocrine tumor
PNET = pancreatic neuroendocrine tumor
SSTR 2 = somatostatin receptor type 2
SPECT = single-photon emission CT
SUV = standard uptake value

pancreatic islets, bronchus, and thymus, which have high penetrance and malignant potential.[2-4] Therefore, 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 with anatomic imaging, traditional radiopharmaceuticals, and endoscopy for gastrointestinal and pancreatic NETs. These radioligands, which include ^{68}Gallium-DOTATATE, ^{68}Gallium-DOTATOC, and ^{68}Gallium-DOTANOC, have a high affinity to somatostatin receptors, especially to type 2 (SSTR 2). A comparison of this new SSTR imaging in a meta-analysis of retrospective studies suggested that ^{68}Gallium-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}Gallium-DOTATATE with ^{68}Gallium-DOTATOC.[6] In the United States, many of these new radioligands are investigational for the detection of NETs. Moreover, the clinical utility of ^{68}Gallium-DOTATATE for screening and or surveillance in patients with MEN1 is unknown.

In this study, we prospectively compared the accuracy of ^{68}Gallium-DOTATATE PET/CT, ^{111}In-pentetreotide single-photon emission CT (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 the presence of primary hyperparathyroidism combined with anterior pituitary tumor and/or gastrointestinal and pancreatic neuroendocrine tumor; a diagnosis of primary hyperparathyroidism combined with a diagnosis of MEN1 in at least 1 first-degree relative; or 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, and bone density by dual energy x-ray absorptiometry, pituitary tumors, and pancreatic and gastrointestinal NETs. Personalized treatment and management are 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, fasting insulin, C-peptide (proinsulin), and glucagon.

Imaging evaluation in patients with MEN1

^{68}Gallium-DOTATATE PET/CT is considered investigational in the United States and is not approved for routine use to localize NETs; therefore, this 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 US Food and Drug Administration. Through a peripheral vein, 5 mCi of ^{68} Gallium-DOTATATE was administered. After approximately 60 minutes, the patient was put in the supine position 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 hours and at 24 hours after intravenous administration of 6 mCi (222 MBq) of ^{111}In-pentetreotide was performed within 4 weeks of ^{68}Gallium-DOTATATE PET/CT, to