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The Role of ^{68}Ga -DOTATATE PET/CT in Well Differentiated Neuroendocrine Tumors: A Case-Based Approach Illustrates Potential Benefits and Challenges

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In 1994, the octreotide scan (somatostatin receptor scintigraphy with ^{111}In -pentetreotide) was approved for imaging of neuroendocrine tumors (NETs) based on studies suggesting that octreotide scans were better at localizing and staging NETs when compared to conventional cross-sectional imaging (computed tomography (CT) and/or magnetic resonance imaging (MRI)).¹ While octreotide scans have the advantage of whole-body visualization, they also have limitations, including low spatial resolution, uptake of the radiotracer in normal organs, and increased burden on patients requiring multiple visits and scans over 2–3 days.²

In 2011, our group evaluated the clinical utility of octreotide scans in detecting additional NET lesions as compared to conventional cross-sectional imaging.³ In our institutional series of 121 patients, cross-sectional imaging detected more NET soft tissue lesions than octreotide scans. Octreotide scans, however, identified more asymptomatic and unsuspected bone metastases. Based on our findings, we concluded that advances made in cross-sectional imaging changed the relative utility of octreotide scans. We advocated for the use of octreotide scans to test for the presence of the somatostatin receptor (SSTR) but not to follow the extent of disease. Although our report was controversial, a subsequent investigation evaluated the clinical utility of octreotide scans in the diagnosis and management of NET patients and also concluded that it did not alter surgical management.⁴ Given these findings, as indicated in the National Comprehensive Cancer Network (NCCN) guidelines, octreotide scans are not recommended for surveillance after resection, as an adjunct for tumor staging, or for monitoring the status of advanced disease.

In recent years, the development of novel functional imaging radioisotopes using PET tracers (the gallium-68 (^{68}Ga) DOTA-peptides: ^{68}Ga -DOTATOC, ^{68}Ga -DOTATATE, ^{68}Ga -DOTANOC) has demonstrated promising results for the visualization of NET lesions in comparison to conventional octreotide scans.^{5–12} Unlike octreotide scans, ^{68}Ga imaging is a

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single-day procedure with higher spatial resolution, improved dosimetry, and the ability to semi-quantify the activity in a given region as the standard uptake value (SUV).¹³

On June 1, 2016, the U.S. Food and Drug Administration (FDA) approved Netspot™, the first kit for the preparation of ⁶⁸Ga-DOTATATE injection for PET imaging, as a diagnostic tool to help clinicians determine the location and extent of NETs. With FDA approval, there has been gradual increase in access to ⁶⁸Ga-DOTATATE PET/CT in the United States, and this scan is now included in the NCCN guidelines as a form of SSTR based imaging. As availability of ⁶⁸Ga-DOTATATE PET/CT increases, it is believed that this imaging will become the gold standard, replacing octreotide scans for the evaluation of SSTR positive disease in patients with NETs.

Despite the advances in SSTR functional imaging, it remains unclear how ⁶⁸Ga-DOTATATE PET/CT will change our clinical practice. Will this scan be used preoperatively to define the extent of disease and alter decisions to operate? Will it replace cross-sectional imaging? Will increased detection of disease alter medical management and importantly, should it? All of these questions remain unanswered. Given the current lack of prospective data to address these questions, we have selected patient cases that we believe illustrate the potential benefits and challenges in using ⁶⁸Ga-DOTATATE PET/CT in the routine clinical setting.

Case 1: First-line treatment options based on presence of SSTR disease

Case 1

A 65-year-old man presented with weight loss and abdominal pain. He underwent a CT scan which demonstrated multiple liver lesions, the largest of which was 4cm in the right hepatic lobe. Upper and lower endoscopies were performed and notable for a tubular adenoma and hyperplastic polyp that were resected. A core liver biopsy demonstrated well differentiated, intermediate grade NET (Ki-67 proliferation index 16%). An upper endoscopic ultrasound was also performed to evaluate for a pancreatic primary lesion, and this study was unremarkable. The patient then underwent octreotide scan which was negative (Figures 1a and 1b). Given this result, he was initially recommended treatment with everolimus or a liver-directed procedure for disease management.

The patient then presented to our institution and was referred for a ⁶⁸Ga-DOTATATE PET/CT, which was performed soon after the octreotide scan, and demonstrated multiple avid foci throughout the liver, consistent with metastases, as well as two avid foci projecting over the small intestine, likely representing the primary tumor versus lymph node metastasis (Figure 2). Given his tumor bulk causing symptoms (pain), the patient began treatment with octreotide LAR with clinical improvement soon after beginning therapy; he is currently on treatment at this time.

Case 1 Discussion

Multiple studies have demonstrated that ⁶⁸Ga-DOTA-peptide PET/CT has a higher detection rate for NET lesions when compared to octreotide scans. Case 1 illustrates this finding. The patient was initially not offered somatostatin analog (SSA) therapy as the disease was not avid on octreotide scan. However, treatment recommendations were changed when ⁶⁸Ga-

DOTATATE PET/CT identified SSTR receptors in the liver and also identified the likely primary in the small bowel.

The results of the PROMID, CLARINET, and NETTER-1 studies demonstrate a clear benefit of the SSTR-directed therapies for symptom control, quality of life, as well as survival.^{14–16} The decision to use SSA or peptide receptor radiotherapy (PRRT) relies on the results from functional imaging demonstrating SSTR positive disease; increased sensitivity to detect SSTR positivity with ⁶⁸Ga-DOTATATE PET/CT, offers more treatment options to the patient.

Cases 2 and 3: Is more better? Use of ⁶⁸Ga imaging in addition to cross-sectional imaging to monitor advanced disease

Case 2

A 61-year-old female initially presented with epigastric and chest pain. CT scan demonstrated a large mass in the pancreatic body and tail as well as a cyst in the liver. In the absence of metastatic disease on cross-sectional imaging, she underwent a distal pancreatectomy and splenectomy, with pathology demonstrating well differentiated, intermediate grade pancreatic NET (Ki-67 proliferation index 15%). Her post-operative course was complicated by a surgical abscess which required debridement. MRI performed for further evaluation of the abscess was concerning for an area of metastatic disease in the liver, and post-operatively, she underwent an octreotide scan which demonstrated a focal region of uptake at the hepatic dome.

The patient fully recovered and presented to our institution. She was initiated on octreotide LAR therapy and her disease remained stable with several months of SSA treatment. Repeat CT triphasic (figure 3) identified an isolated liver metastasis and possible surgical resection was discussed. Prior to surgical evaluation, she underwent ⁶⁸Ga-DOTATATE PET/CT, and this study unfortunately demonstrated avidity in the hepatic dome lesion, as well as additional left and right hepatic lobe lesions (Figure 4). MRI liver was then performed and identified the hepatic dome metastasis, as well as punctate lesions corresponding to the foci of uptake seen on PET (Figure 5). Given these findings, surgery was not pursued and she remains on systemic therapy at this time.

Case 3

A 56-year-old man presented with an abnormal chest x-ray. Subsequent work-up included a CT scan which demonstrated a left lower lobe tumor. He underwent surgical resection, with pathology demonstrating an atypical lung NET (mitotic rate 3/10 high power fields, surgical margins negative, three of seven lymph nodes positive).

Three years after surgery, the patient was found to have new bilobar liver lesions on surveillance cross-sectional imaging, with biopsy demonstrating recurrent NET, intermediate grade (Ki-67 proliferation index 5–10%). Octreotide scan was performed, demonstrating SSTR-positive disease in the liver and bone, and the patient was initiated on octreotide LAR. He was maintained on octreotide LAR with minimal disease growth for 2.5 years, prior to

radiographic progression. At the time of progression, CT chest and MRI Liver were performed, and, through a clinical trial open at our institution, the patient underwent ^{68}Ga -DOTATOC PET/CT (Figure 6). CT chest demonstrated a left pleural nodule as well as T12 vertebral metastasis. MRI liver demonstrated multiple enlarging hepatic metastases and several unchanged osseous metastases. ^{68}Ga -DOTATOC PET/CT again identified SSTR-positive disease in the bone, liver, and the pleural based lung nodule, but also detected avid posterior mediastinal paraesophageal lymph nodes. Given these findings, the patient received PRRT for disease management.

Case 2 and 3 Discussion

Due to improved sensitivity, ^{68}Ga imaging can sometimes uncover an increased burden of disease, in comparison to cross-sectional imaging. In Case 2, ^{68}Ga -DOTATATE PET/CT imaging picked up additional liver disease and surgery was not pursued. In Case 3, the patient received both cross-sectional imaging as well as a ^{68}Ga -DOTATOC PET/CT at the same time-point, and ^{68}Ga -DOTATOC PET/CT identified additional lymph node disease. Case 2 illustrates the important role ^{68}Ga -DOTATATE PET/CT imaging can play in altering treatment while the additional disease identified in Case 3 did not alter management.

Could ^{68}Ga -DOTATATE PET/CT imaging potentially replace cross-sectional imaging? To date, we have no prospective data directly comparing the two modalities in reassessing and monitoring advanced disease. However, it is well recognized and accepted that, for any surgical debulking or liver-directed procedures, which are frequently used for disease management in NETs, an understanding of the anatomy is essential and is currently only available through cross-sectional imaging. It is possible to perform cross-sectional imaging (i.e. liver triphasic CT scan) at the same time as ^{68}Ga imaging and this approach may provide an option to both characterize SSTR status and disease anatomy together. These are important questions to address in future research efforts.

Other Important Points to Consider

1. *^{68}Ga -DOTATATE PET/CT for surveillance after resection:* To date, studies have not directly compared sites of NET disease identified by ^{68}Ga -DOTATATE PET/CT to those identified by cross-sectional imaging in the setting of surveillance after resection. For this reason, there is currently no data to clarify or support a role for ^{68}Ga -DOTATATE PET/CT for surveillance in the adjuvant setting.
2. *Insurance coverage and reimbursement of costs for patients receiving ^{68}Ga -DOTATATE PET/CT:* The FDA-approval of NetspotTM allows any nuclear medicine facility with PET-CT scanning ability to perform ^{68}Ga -DOTATATE PET/CT imaging. In the United States, ^{68}Ga -DOTATATE PET/CT is not widely available at all nuclear medicine facilities. Furthermore, despite FDA approval and inclusion in the 2017 NCCN guidelines as a diagnostic study, coverage for ^{68}Ga -DOTATATE PET/CT is not routine for all insurance plans. As our use of ^{68}Ga -DOTATATE PET/CT increases for patients with NETs, the financial toxicity of this imaging modality will require review.

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FIGURE 1.

A, Octreotide scan negative at 4 hours. B, Octreotide scan negative at 24 hours.

FIGURE 2.
SSTR avidity in liver and small bowel on ^{68}Ga -DOTATATE PET/CT.

FIGURE 3.
Only hepatic dome lesion visualized on liver triphasic CT.

FIGURE 4.
SSTR avidity in liver on ^{68}Ga -DOTATATE PET/CT.

FIGURE 5.
MRI liver with punctate lesion correlating with ^{68}Ga -DOTATATE PET/CT.

FIGURE 6.

In addition to lung, liver, and bone disease, thoracic lymph node disease also identified on ⁶⁸Ga-DOTATOC PET/CT.