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EDITORIAL – ENDOCRINE TUMORS

The Supporting Role of ^{18}FDG-PET in Patients with Neuroendocrine Tumors

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There has been a marked, unexplained increasing incidence of neuroendocrine tumors (NETs) over the past few decades. This may be due to a combination of different factors, such as changes in the environment with new exposures to injurious agents or an increased awareness of these neoplasms, but perhaps most of all, improvements in and utilization of body imaging. It has been estimated that as many as 72 million computed tomographic (CT) scans are done per year in the United States, a threefold increase since 1993.[1] Abdominal CTs will detect liver metastases, and metastatic disease is found in 30 % of patients with small bowel NETs and 64 % of those with pancreatic NETs.[2] Primary pancreatic NETs are commonly seen on CT if they are greater than 1 cm in size and appropriate administration of intravenous contrast is given. Primary small bowel NETs are more subtle because they are frequently small and intramural. They may show up as thickening of the bowel wall or a mass, but more commonly, one may see enlarged, calcified nodes in the mesentery.

Although anatomic imaging (CT, MRI) has been very useful, the finding of a mass in the pancreas, mesentery, or liver does not define a tumor as being neuroendocrine in origin. This is where functional imaging for NETs can be useful. For these studies, octreotide is conjugated to a radioisotope, which accumulates in areas with a high density of somatostatin type 2 (SST2) receptors, which are expressed on the cell membranes of the majority of NETs. This has evolved into the exam we know today as OctreoScan, where patients are given an intravenous injection of ^{111}In-octreotide, and then scintigraphy is performed at 4 and 24 h. One important early study optimistically quoted finding uptake in 96 % of small bowel and 68 % of pancreatic NETs, but never specified whether the uptake seen was in primary tumors or their metastases.[3] Nevertheless, this imaging modality has turned out to be useful in NETs from a multitude of primary sites, as long as they express SST2 receptors. Improvements have come over time with the administration of a bowel preparation before imaging, combining with single-photon emission computed tomography (SPECT), and more recently, by coregistration with CT scans. One recent study evaluating OctreoScans in patients with surgically confirmed small bowel NETs found that either the primary tumor or adjacent nodes had uptake in 74 % of cases, and liver metastases in 66 % (of cases where metastases were present).[4]

Functional imaging for NETs has used other agents over the years, including ^{123}I-Tyr^3-octreotide and ^{123}I-MIBG, in addition to the standard of ^{111}In-octreotide. A more contemporary improvement has come from combining functional imaging with positron emission tomography (PET). The advantage of PET over SPECT is that the latter relies on detection of single photons, which are emitted in all directions. In PET, the decay of a positron causes the emission of two photons in opposite directions, which allows for significant improvement in resolution and precise quantitative imaging. The most useful scans for patients with NETs have been a PET scan using the positron emitter ^{68}Ga conjugated to DOTA-modified octreotide (DOTA-TATE or DOTATOC). Imaging can be done with less radiation exposure, and in just 1 h instead of 2 days with significantly improved resolution as compared to OctreoScan.[5] In addition, like OctreoScan, it helps to predict those likely to respond to peptide radioreceptor therapy for these tumors. Although widely available in Europe for the last decade, there have been barriers to its use and adoption in the United States because it is not

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approved for clinical use by the US Food and Drug Administration. Published safety data on ^{68}Ga-DOTA-modified octreotide analogs is scarce; however, the literature suggests few, if any, adverse events with the use of these PET imaging agents. For this reason, only a few centers have been able to use this investigational pharmaceutical for imaging in the United States.

The PET imaging modality that is widely available in the United States is ^{18}F-fludeoxyglucose (^{18}FDG)-PET, and experience has been accumulating with its use in NET patients. Uptake in these scans is not specific for NETs but rather takes advantage of the fact that hypermetabolic tissues (such as tumors) take up glucose. Several studies have shown that ^{68}Ga-DOTA-modified octreotide PET has improved sensitivity in well-differentiated NETs over ^{18}FDG-PET, while the latter performed better in high-grade NETs.[6] For patients being treated in the United States, the more relevant comparison is that of OctreoScan versus ^{18}FDG-PET, and to date, there have only been a few studies comparing the results of these imaging modalities in patients with NETs.

In this issue, Squires et al. performed a single-institution retrospective review comparing the results of OctreoScan and ^{18}FDG-PET in 153 patients with gastrointestinal (GI) or pancreatic NETs who were explored between 2000 and 2013.[7] Of these, the majority had OctreoScans (86 %; 131 of 153), 28 % (43 of 153) had ^{18}FDG-PET, and 14 % (21 of 153) had both studies performed. Of these patients, 33 % ($n = 50$) had pancreatic NETs, 20 % ($n = 30$) jejunoileal NETs, and 38 % ($n = 58$) NETs from other GI sites (duodenal, gastric, ampullary, and colorectal); 15 % ($n = 23$) of patients had liver metastases after resection of a GI or pancreatic primary, and 8 % ($n = 12$) had liver metastases and a lesion of unknown primary. In this last group, imaging did not find the primary lesion in any of these patients, and only one tumor was found at exploration, illustrating the challenge of NETs of unknown primary site. With respect to World Health Organization tumor grade, 62 % ($n = 94$) patients had grade 1, 27 % ($n = 42$) had grade 2, and 11 % ($n = 17$) had grade 3 tumors. The sensitivity of OctreoScan was found to be 80 % (99 of 124) for well-differentiated NETs but only 57 % (4 of 7) for poorly differentiated NETs. The sensitivity for ^{18}FDG-PET was lower for well-differentiated NETs (60 %, 18 of 30) but improved to 100 % (13 of 13) for poorly differentiated NETs. In well-differentiated NETs, ^{18}FDG-PET performed as well as OctreoScan for pancreatic NETs (sensitivity of 75 vs. 73 %, respectively) but significantly worse for GI NETs (38 % sensitivity compared to 84 % with OctreoScan). They also demonstrated that the 5-year overall survival of patients with ^{18}FDG-PET-positive tumors was significantly worse than those with negative tumors (40 vs. 100 %; $p = 0.006$). It should be noted that a relatively low threshold of >2.5 standardized uptake value was used to define an ^{18}FDG-PET scan as positive. The authors confirm what we know about ^{18}FDG-PET in NETs: that a positive scan is commonly associated with poor differentiation and a higher risk of recurrence.

Other studies directly comparing OctreoScan and ^{18}FDG-PET in patients with GI and pancreatic NETs have arrived at similar findings. Binderup et al. found an overall sensitivity of 89 % with OctreoScan and 58 % with ^{18}FDG-PET in 96 NET patients. However, in 13 patients with tumors with a Ki-67 of >15 % (with high grade being defined as >20 %), the sensitivity of ^{18}FDG-PET was 92 % versus 69 % for OctreoScan.[8] Garin et al. evaluated ^{18}FDG-PET and OctreoScan in 38 patients with metastatic NETs and found that 14 of 15 patients who were ^{18}FDG-PET positive had early disease progression (defined as within 6 months) versus 2 of 23 who were ^{18}FDG-PET negative. Even in the subset of patients with low-grade tumors, in 12 of 34 who had early progression, the ^{18}FDG-PET was positive in 10 of 12. Patients with negative OctreoScans also had early progression (9 of 11 patients), while this was only seen in 7 of 27 with positive OctreoScans. Two-year overall survival was 95 % for ^{18}FDG-PET-negative patients and 42 % when they were positive, compared to 70 % in OctreoScan-positive patients and 60 % in OctreoScan-negative patients.[9]

These studies, and the current work of Squires et al. demonstrate that the utility of ^{18}FDG-PET in NETs is in the identification of high-grade tumors and in predicting which low-grade tumors will go on to have rapid progression and worse overall survival. This information is useful for determining those patients who might benefit most from surgery versus those in whom medical management (other than octreotide) will play a major role, such as patients with high-grade tumors at risk for early progression. Not all NET patients need to have an ^{18}FDG-PET scan, but it should be carefully considered when they have a negative OctreoScan or when a biopsy sample reveals a high-grade tumor.

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