PET in Evaluation of Neuroendocrine Tumors

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Neuroendocrine tumors (NETs) are distinctive tumors which arise from cells which have neural and hormonal origins. The most common clinically-encountered NETs are gastroenteropancreatic tumors (GEP NETs), lung carcinoids, pheochromocytoma, and medullary thyroid carcinoma. Imaging plays a key role in the evaluation of these tumors including detection, staging, response assessment, and prognostication. Conventional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) are still the first line imaging modalities used in the evaluation of these tumors. Radionuclide imaging of NETs is done with either planar imaging (with or without single photon emission computed tomography (SPECT)) or with positron emission tomography (PET). PET imaging offers many advantages over planar or SPECT imaging which includes better resolution, a better background-to-lesion ratio, and increased sensitivity. Fusion with CT greatly improves specificity and diagnostic confidence. Various PET tracers are available for evaluation of NETs of which F-18-fluorodeoxyglucose (F18 FDG), F-18-fluorolevodopa (F18 FDOPA), and Ga-68 somatostatin receptor (SST) imaging agents (e.g. DOTATATE, DOTATOC and DOTANOC) are currently the most widely used. In this brief review, we describe the role of these PET tracers in evaluation of NETs with an emphasis on (GEP NETs).
Physiological basis and characteristics of NETs targeted for PET imaging:

1) Increased anaerobic metabolism and glucose transporter expression – F18 FDG. This phenomenon is seen more often in dedifferentiated tumors than with well-differentiated NETS.

2) Increased production, decarboxylation of amines, with increase in uptake of amine precursors like Di-hydroxyphenylalanine (DOPA) - F18 FDOPA.

3) Increased expression of somatostatin receptors - Ga-68 DOTATE and Ga-68 DOTANOC.

F-18 FDG PET/CT:

F18-FDG is a fluorinated analogue of deoxyglucose, and the uptake in tumor cells is based on increased anaerobic metabolism with increased GLUT transporter expression. This phenomenon is seen more often in dedifferentiated NETS than in well-differentiated tumors. Administered doses are typically 370-740 MBq (10-20 mCi) intravenously followed by whole-body acquisition with PET and CT after 60 minutes. Physiological F18 FDG uptake is seen in brain, salivary glands, myocardium, liver, spleen, bowel, and urinary system (kidneys and urinary bladder). F18 FDG PET/CT has conventionally thought to have a limited role in the evaluation of NETs especially in detection and staging. This is due to the fact that well-differentiated NETS are slow growing and do not concentrate F18 FDG. F18 FDG PET has been shown to have a very low sensitivity of 57% in detecting well-differentiated carcinoid tumors (1). However, dedifferentiated tumors show increased F18 FDG uptake, and the degree uptake of F18 FDG was shown to correlate with Ki-67 expression (a marker of proliferation). In a study by Kayani et al, it was shown that F18 FDG uptake was more often seen in patients with a Ki-67 of 20 or more (2). In another study by Abgral et al (3), it was
shown that F18 FDG PET had better performance than typical (non-PET) somatostatin receptor scintigraphy (SRS), and that combined F18 FDG PET with CT had an accuracy of 87% for detecting lesions in patients with metastatic NETs and a high Ki-67 index of 10 more. During the process of dedifferentiation, NETs lose their ability to concentrate somatostatin analogues and tend to show an increased concentration of F18 FDG. This phenomenon has been called tumor “flip flop” and infers poorer prognosis. In a prospective study by Garin et al which included 38 patients with metastatic NETs, negative SRS and positive F18 FDG PET/CT correlated with poorer prognosis. In this study, F18 FDG PET/CT had excellent negative and positive predictive values of 91% and 93% for early progression (< 6 months) (4). To conclude, F18 FDG PET/CT is not an ideal imaging modality for the detection and staging of NETs but has a potential role in tumor grading and prognostication and in identifying patients who may benefit from systemic chemotherapy versus somatostatin-based therapies.
There is a focus of increased uptake in the left upper abdomen on the MIP image. This correlates to a hypermetabolic focus in the spleen on the axial views and consistent with metastatic disease in this patient with known prior uterine cervix NET. Additional metastatic lesions in the lungs and a few lymph nodes is seen on the MIP image.
F-18 FDOPA PET/CT:

F18 FDOPA is a fluorinated analogue of the catecholamine precursor DOPA and is actively taken up by cells where there is increased production and decarboxylation of amines. The typical dosage of F18 FDOPA is 370 MBq (10mCi) administered intravenously. Images are acquired 60 minutes after administration of the radiotracer. Physiological F18 FDOPA uptake is seen in the striatum of the brain, gallbladder, and urinary system (kidneys and urinary bladder). One of the major advantages of F18 FDOPA is its biodistribution with very minimal uptake seen in normal tissues which provides an excellent lesion-to-background ratio. F18 FDOPA PET was shown to be highly sensitive and specific in the detection of NETs as well as in lymph nodes, skeletal, and liver metastases with statistically better performance than CT and SRS on a lesion-based analysis (5). F18 FDOPA PET/CT also has a potential role in the detection of primary NETs of unknown origin (CUP-NET). Detection of this primary is important in this group of patients as localization and surgical resection of the primary offers the best chance of curative treatment. In a recent study by Imperiale et al, F18 FDOPA PET showed promising results in this aspect. In this study with 27 patients with negative SRS and conventional imaging, F18 FDOPA PET detected primary tumors in 12 patients and was falsely negative in two patients (6). Also and more interestingly, patients with a positive F18 FDOPA PET had high levels of serum chromogranin and serotonin and high urinary excretion of 5-hydroxyindolacetic acid (5-HIAA) when compared to those with a negative study (6). This important finding might have clinical implications when choosing an appropriate imaging modality in patients with CUP-NET depending on the levels of biomarkers. Another potential role of F18 FDOPA PET is in the evaluation of hyperinsulinism of infancy. Differentiation of focal and diffuse forms of the disease is important as surgical treatment differs drastically from
local excision to subtotal or total pancreatectomy. F18 FDOPA PET also has the advantage of being a noninvasive test and is by far the most promising imaging modality in this context. In contrast to this, pancreatic venous sampling (PVS), though an accurate method for identifying focal pancreatic lesions and directing surgery, is an invasive technique and a technically challenging procedure. In a retrospective study of 47 patients, it was shown that F18 FDOPA PET was concordant with PVS in 11/12 patients and surgical findings correlated with F18 FDOPA PET findings in 21/24 patients (7).

Image 2 (F18 FDOPA):

A: MIP; B: Axial PET; C: Axial Contrast-Enhanced CT; D: Fused PET and CT

There is focal F18 FDOPA accumulation in the pancreas in this patient who was evaluated for congenital hyperinsulinism of infancy. (Images courtesy of Dr. Amol Takalkar).
Ga-68 SST PET/CT:

Ga-68 DOTANOC and Ga-68 DOTATATE are the two of the more common gallium analogues used in the evaluation of NETs. Their mechanism of uptake in neuroendocrine cells is due to the increased expression of SST and is also the basis of imaging with somatostatin receptor scintigraphy (SRS). Ga-68 DOTATATE has a high affinity for SST2 receptors (with a much lower affinity for a few other receptor types), while Ga-68 DOTANOC has a different affinity profile also targeting SST2 as well as SST3 and SST5 receptors (though the affinity for SST2 is not as high as that of DOTATATE). (See Image 3 for more information on receptor affinity).

Limited literature exists comparing the performance of the various Ga-68 SST tracers. In a small study including 18 patients, Wild et al demonstrated that lesion-based sensitivity, especially for liver metastases, was higher with Ga-68 DOTATOC when compared to Ga-68 DOTATATE (8). Further larger studies are required to help understand the differences in performance of these two tracers. Typical administered doses are 100-200 MBq (3-6 mCi) via an intravenous route for both the tracers. Images are acquired 60 minutes after injection. Physiological uptake is seen in liver, spleen, pituitary, thyroid, kidneys, adrenal glands, salivary glands, stomach wall, and bowel. Variable uptake (although frequently focal) is also seen in pancreas. In addition, the breasts and prostate gland may show diffuse uptake. Multiple studies have shown the potential role of these tracers in staging and detection of recurrences in NETs. Hoffman et al first described the potential role of Ga-68 somatostatin analogues and demonstrated their superiority over SRS in evaluation of NETs (9). Haug et al in a study which included 63 patients, demonstrated that Ga-68 DOTATATE had a sensitivity of 90% and specificity of 82% in detecting recurrent NET. Naswa et al evaluated the role of Ga-68 DOTATOC in evaluation of CUP-NET and showed a sensitivity of 60% in localizing the primary
tumor which also helped change management. Also, a change in management was noted in 15% of the patients when compared to conventional imaging. An additional potential role of Ga-68 DOTATATE/DOTATOC imaging is prognostication of patients with NETs. SUVmax values correlate inversely with the grade of tumor, and when combined with F18 FDG PET, may identify patients who need systemic chemotherapy versus somatostatin or peptide receptor radionuclide therapy (PRRT) (4, 10). Ga-68 DOTATOC/DOTATATE PET/CT has also been used to evaluate the response to PRRT. However, reduction in SUVmax of tumors on follow-up may not always correlate with the actual response. As described earlier, reductions in SUVmax of NETs may also suggest dedifferentiation. Therefore, it is important to realize this potential pitfall in assessing response. Haug et al in a study which included 33 patients showed that reduction in an SUVmax/splenic SUVmax ratio was found to correlate with response when compared to SUVmax reduction (11). Image 4 below also gives a summary utilizing G-68 DOTATOC PET vs SPECT vs CT.
Ga68 DOTANOC

68Ga-DOTA-conjugated peptides are used for the assessment of somatostatin (SST) receptor-expressing tumors based on the high affinity of these compounds for SST receptors (SST is a small, cyclic neuropeptide).

- 68Ga-DOTA0-Tyr3[octreotide (68Ga-DOTA-TOC)
- 68Ga-DOTA0-1NaI3[octreotide (68Ga-DOTA-NOC)
- 68Ga-DOTA0-Tyr3[octreotate (68Ga-DOTA-TATE)

Note: the smaller the number the higher the affinity for the receptor


Ga68 DOTATOC vs SPECT vs CT

TABLE 5
Comparison of 3 Imaging Modalities: PET, SPECT, and CT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PET (%)</th>
<th>SPECT (%)</th>
<th>CT (%)</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>97 (69/71)</td>
<td>52 (37/71)</td>
<td>61 (41/67)</td>
</tr>
<tr>
<td>Specificity</td>
<td>92 (12/13)</td>
<td>92 (12/13)</td>
<td>71 (12/17)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>96 (81/84)</td>
<td>58 (49/84)</td>
<td>63 (53/84)</td>
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CONCLUSION

Somatostatin receptor PET with 68Ga-DOTA-TOC is superior for the detection of NET compared with SPECT and diagnostic CT in various clinical situations (initial diagnosis, staging, and follow-up). The higher sensitivity for tumor detection has clinical impact in a considerable number of patients, especially when compared with CT. However, the best results are to be achieved by the combination of PET and CT. It also indicates receptor expression for targeted radioligand therapy.
A: PET whole-body MIP; B: Axial PET; C: Fused Axial PET and CT

There is intense Ga-68 DOTATATE uptake in the liver (blue arrows), sigmoid colon (purple arrows), and in the rectal wall (green arrows). Intense uptake is also noted in perirectal lymph nodes on the axial views. These findings are consistent with primary rectosigmoid malignancy with extensive metastatic disease to the liver and also to perirectal lymph nodes. Of note, physiologic uptake is seen in the spleen and bladder, and trace normal activity is seen in bowel elsewhere.
References:


