SNMMI AUC Factsheet for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors

EXECUTIVE SUMMARY

Nuclear medicine imaging studies are essential for the diagnosis and management of many diseases, including neoplastic disease. The ready availability of medical imaging studies in conjunction with concerns about missed diagnoses has, at times, resulted in inappropriate use and overuse of medical imaging technology, including nuclear imaging. The overuse has resulted in an unnecessary financial burden on the health-care system and in some cases unnecessary exposure to ionizing radiation. Overuse and inconsistent use of imaging procedures has prompted a push for multi-stakeholder consensus documents outlining the most appropriate and cost-effective use of advanced medical imaging studies.

It is hoped that this document, developed by medical experts knowledgeable in the appropriate use of somatostatin receptor PET imaging, will improve healthcare outcomes for the intended patient population while helping to decrease unnecessary imaging costs.

AUC INTRODUCTION

The purpose of this document is to describe the appropriate use of somatostatin receptor (SSTR) PET imaging in neuroendocrine tumors (NETs). NETs are relatively rare and develop most commonly in the lungs, appendix, small intestine, rectum, and pancreas. Many NETs start in the digestive tract, as it has more neuroendocrine cells than any other part of the body. Some tumors grow slow while others can be very aggressive and spread to other parts of the body, most often the liver or bone.

The most common clinical scenarios for PET imaging for neuroendocrine tumors are listed in the chart below; however, the reader is reminded that patients may present with variations of the scenarios covered here, with signs or symptoms not described. Each patient is unique, as is each clinical presentation, and therefore this document cannot replace clinical judgment. Somatostatin receptor PET imaging can also be used for other malignant and benign conditions for which assessment is important for patient management. These other scenarios are beyond the scope of this document.

There are several types of NETs. Treatment and imaging depends on the type of tumor and its location, whether it produces excess hormones, how aggressive it is, and whether it has spread. Recommendations for the appropriate use of somatostatin receptor PET imaging in neuroendocrine tumors are described in this AUC.

BACKGROUND ON SSTR-PET

Somatostatin is a naturally occurring hormone that acts by binding to somatostatin receptor (SSTR), a receptor that is overexpressed on most NETs. Somatostatin analogs (SSAs) such as octreotide and lanreotide exert their therapeutic effects by activating SSTRs, which slow tumor growth and inhibit tumor associated hormone secretion. The presence of SSTRs can be imaged by labeling somatostatin analogs with a radionuclide.

New imaging agents targeting SSTR labeled with Gallium 68 have recently been developed (DOTATATE and DOTATOC).* ^{68}Ga-DOTATATE (NETSPOT, Advanced Accelerator Applications), ^{68}Ga-DOTATOC and ^{64}Cu-DOTATATE (Detectnet, Curium) are currently approved by the Food and Drug Administration. These newer imaging agents provide tumor detection sensitivity, improved patient convenience due to the 2-hour imaging time, decreased radiation dose, decreased biliary excretion and the ability to calculate uptake. Human dosimetry (radiation exposure) data for Gallium 68 imaging agents and the estimated total body radiation dose per administered activity have been measured at 4.3 and 4.8 mSv. No adverse events have been reported in association of SSTR-PET agents.

TABLE 2: CLASSIFICATION OF GASTROENTEROPANCREATIC NETs: SUMMARY OF RECOMMENDATIONS

NETs vary in tumor aggressiveness, and tumors are categorized by histologic evaluation. Precise rules for classification vary by tumor site or origin. Gastroenteropancreatic NETs are typically classified on the basis of the Ki-67 proliferation index or the mitotic count (the number of cells dividing in a certain amount of cancer tissue). Well differentiated, G1 and G2 (cancer cells that tend to grow and spread more slowly) are measured in years even in the face of metastatic disease. High grade, G3, poorly differentiated neuroendocrine carcinomas (NECs) are typically much more aggressive and have almost always metastasized by the time it is diagnosed. Tumors that are identified as well differentiated G3 NETs are thought to have an intermediate prognosis (closer to traditional well differentiated NETs). SSTR-PET is used primarily in G1 and G2 tumors, while G3 tumors are frequently better imaged using FDG PET.

TABLE 2: Classification of Gastroenteropancreatic NETs

Differentiation	Grade	Ki-67 index	Proliferative rate	SSTR PET positivity
Well differentiated	Low grade (G1)	<3%	<2 mitoses/10 hpf	+++
	Intermediate grade (G2)	3%-20%	2-20 mitoses/10hpf	++
Poorly differentiated	High grade (G3)	>20%	>20 mitoses/20 hpf	Variable*

hpf: high-power field.

*In high-grade NETs, SSTR positivity is variable, and frequently 18F-FDG PET performs better as an imaging study in patients with these NETs. SSTR PET results may be positive for well-differentiated G3 tumors, and imaging may be helpful in finding patients who are candidates for PRRT.

Table 3 CLINICAL SCENARIOS FOR SSTR PET: SUMMARY OF RECOMMENDATIONS

Clinical scenarios for the use of SSTR-PET and final AUC scores in patients with NETs are presented in Table 3. In grading clinical indications, we focused on well-differentiated NETs. SSTR-PET is generally indicated in patients at time of initial staging. SSTR-PET can locate the primary tumor site and often demonstrates additional lesions not captured by conventional imaging (CT or MRI), resulting in better staging that results in clinically relevant changes in management in about one third of patients. However, it is important to recognize that identification of ore extensive disease may not always have an impact on clinical management and may increase patient and provider anxiety by demonstrating more disease burden than previously visualized with conventional testing. As with other novel imaging modalities, it is important for physicians and patients to realize that direct comparisons between SSTR-PET and other imaging tests are not equivalent, and what appears to be disease progression on the first SSTR-PET study may simply represent more accurate staging, disease progression being confirmed only by comparing like scans over time.

As a tool for monitoring patients over time, conventional imaging (CT and/or MRI) should be considered as they more accurately depict changes in size of tumor that is valuable in determining treatment response. At time of progression, SSTR-PET can be helpful in determining if a patient would be a candidate for peptide receptor radionuclide therapy (PRRT). PRRT is a newly approved treatment for NETs, that requires the presence of SSTRs to be effective.

TABLE 3: Clinical scenarios for SSTR-PET

Scenario no.	Description	Appropriateness	Score
1.	Initial staging after the histologic diagnosis of NET.	*Appropriate*	9
2.	Localization of primary tumor in patients with known metastatic disease, but an unknown primary.	*Appropriate*	9
3.	Selection of patients for somatostatin-receptor targeted PRRT	*Appropriate*	9
4.	Staging NET prior to planned surgery.	*Appropriate*	8
5.	Evaluation of a mass suspicious for NET not amenable to endoscopic or percutaneous biopsy (for example: ileal lesion, hypervascular pancreatic mass, mesenteric mass etc.).	*Appropriate*	8
6.	Monitoring of NET seen predominantly on SSTR-PET	*Appropriate*	8
7.	Restaging of patients after the completion of PRRT	*Appropriate*	7
8.	Evaluation of patients with biochemical evidence and symptoms of a NET without evidence of NET on conventional imaging without a prior histologic diagnosis of NET.	*Appropriate*	7
9.	Restaging at time of clinical or laboratory progression without progression on conventional imaging	*Appropriate*	7
10.	New indeterminate lesion on conventional imaging, with unclear progression	*Appropriate*	7
11.	Restaging of patients with NET at initial follow-up after resection with curative intent	*May be appropriate*	6
12.	Selection of patients with non-functional NETs for somatostatin analog treatment	*May be appropriate*	6
13.	Monitoring in patients with NET seen on both CI and SSTR-PET with active disease and no clinical evidence of progression	*May be appropriate*	5

*DOTATATE and DOTATOC are analogs of the somatostatin hormone which, when bound to gallium-68 or copper-64, can be used to image somatostatin receptor positive tumors.

**Table numbers are listed in as found the full AUC document.

This AUC was developed with participation from experts affiliated with the following organizations: American College of Radiology, American Society of Clinical Oncology, North American Neuroendocrine Tumor Society, European Association of Nuclear Medicine, Endocrine Society, Society of Surgical Oncology, National Comprehensive Cancer Network, NorCal CarciNET Community, American College of Physicians, American Gastroenterological Association, and Society of Interventional Oncology.

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