Journal of Nuclear Medicine, published on October 12, 2017 as doi:10.2967/jnumed.117.202275

Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors

Thomas A. Hope[1,2*], Emily K. Bergsland[3,4], Murat Fani Bozkurt[5], Michael Graham[1], Anthony P. Heaney[6], Ken Herrmann[5], James R. Howe[4,7], Matthew H. Kulke[3,4,8], Pamela L. Kunz[3,4,8], Josh Mailman[9], Lawrence May[10], David C. Metz[4,11], Corina Millo[1], Sue O'Dorisio[1,3,4], Diane L. Reidy-Lagunes[3,4], Michael C. Soulen[4,12], and Jonathan R. Strosberg[3,4]

[1]Society of Nuclear Medicine and Molecular Imaging; [2]American College of Radiology; [3]American Society of Clinical Oncology; [4]North American Neuroendocrine Tumor Society; [5]European Association of Nuclear Medicine; [6]Endocrine Society; [7]Society of Surgical Oncology; [8]National Comprehensive Cancer Network; [9]NorCal CarciNET; [10]American College of Physicians; [11]American Gastroenterological Association, [12]World Conference on Interventional Oncology

Running title: Somatostatin Receptor PET AUC

Corresponding and First Author:
Thomas A. Hope, MD
505 Parnassus Avenue – 0628
Department of Radiology and Biomedical Imaging
University of California, San Francisco
San Francisco, CA 94143-0628
Phone: (415) 353-1905
Email: thomas.hope@ucsf.edu

EXECUTIVE SUMMARY

Somatostatin receptor positron emission tomography (SSTR-PET) is an imaging modality for patients with neuroendocrine tumors (NETs) that has demonstrated a significant improvement over conventional imaging (CI). SSTR-PET should replace In-111 pentetreotide scintigraphy (OctreoScan) in all indications in which SSTR scintigraphy is currently being used. These appropriate use criteria (AUC) are intended to aid referring medical practitioners in the appropriate use of SSTR-PET for imaging of patients with NETs, and the indications were evaluated in well-differentiated NETs. Of the 12 clinical scenarios evaluated, nine were graded as appropriate: initial staging after the histologic diagnosis of NET, evaluation of an unknown primary, evaluation of a mass suggestive of NET not amenable to endoscopic or percutaneous biopsy, staging of NET prior to planned surgery, monitoring of NET seen predominantly on SSTR-PET, evaluation of patients with biochemical evidence and symptoms of a NET, evaluation of patients with biochemical evidence of a NET without evidence on CI or a prior histologic diagnosis, restaging at time of clinical or laboratory progression without progression on CI, and new indeterminate lesion on CI with unclear progression. Representatives from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the American College of Radiology (ACR), the American Society of Clinical Oncology (ASCO), the North American Neuroendocrine Tumor Society (NANETS), the European Association of Nuclear Medicine (EANM), the Endocrine Society, the Society of Surgical Oncology, the National Comprehensive Cancer Network (NCCN), the American College of Physicians (ACP), the American Gastroenterological Association (AGA), and the World Conference on Interventional Oncology (WCIO) assembled under the auspices of an autonomous workgroup to develop the following AUC.

INTRODUCTION

Neuroendocrine Tumors (NETs)

NETs are relatively rare and encompass a heterogeneous group of tumors with an incidence of approximately 7.0 in 100,000 (*1,2*), although it is increasing. The most common type are gastroenteropancreatic (GEP)-NETs, which are broken down by sites of origin into gastric, pancreatic, small bowel, colorectal, and those of unknown origin. In addition to GEP-NETs, there are a large number of subtypes of NETs, including pheochromocytomas, paragangliomas, medullary thyroid cancer, merkel cell cancer, and bronchial carcinoids. Given the lack of evidence in other disease subtypes, these AUC will focus on the role of SSTR-PET in well-differentiated GEP-NETs. Although not covered in the clinical scenarios in this document, the belief is that SSTR-PET will be valuable in many SSTR-positive diseases beyond GEP-NETs.

Somatostatin Receptor (SSTR)

Somatostatin is a naturally occurring hormone that acts by binding to SSTR, a receptor that is overexpressed on most NETs. There are 5 predominant subtypes of SSTR, type 2 being the most commonly expressed in NETs (*3*). Somatostatin analogs (SSAs) such as octreotide and lanreotide exert their therapeutic effects by activating SSTRs, which slows tumor growth and inhibits tumor-associated hormone secretion. The presence of SSTRs can be imaged by labeling SSAs with a radionuclide, which

was originally performed with octreotide, an octapeptide SSA (*4–6*). In-111 pentetreotide (OctreoScan) was the standard imaging modality for staging and characterizing NETs prior to SSTR-PET.

SSTR-PET

Newer imaging agents targeting SSTR labeled with gallium-68 have subsequently been developed, namely, DOTATATE and DOTATOC (*7*). ^{68}Ga-DOTATATE (NETSPOT, Advanced Accelerator Applications) is currently approved by the Food and Drug Administration. A New Drug Application for ^{68}Ga-DOTATOC is being developed by the University of Iowa. These agents have a number of benefits over In-111 pentetreotide, including improved detection sensitivity, improved patient convenience due to the 2-hour length of study, decreased radiation dose, decreased biliary excretion due to earlier imaging after radiotracer administration, and the ability to quantify uptake. This AUC document focuses on ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC, which are collectively referred to as SSTR-PET. Little head-to-head data are available that compare different SSTR-PET agents, but no relevant differences have been demonstrated between the 2 agents when used for imaging (*8,9*). In general, the workgroup agreed that for all indications for which In-111 pentetreotide is used, it should be replaced with SSTR-PET.

Safety and Dosimetry of SSTR-PET

Human dosimetry data for ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC have been reported (*10,11*), and the estimated total body radiation dose is 4.8 mSv for ^{68}Ga-DOTATATE and 4.3 mSv for ^{68}Ga-DOTATOC for a 185 MBq (5 mCi) administration (Table 1). No adverse events have been reported in association with the administration of SSTR-PET agents (*12*).

Use of Intravenous Contrast With SSTR-PET

Standard PET/CTs have frequently been performed without the administration of intravenous contrast. The use of intravenous contrast has been shown to increase the detection rate of liver metastases for ^{18}F-FDG PET as well as for SSTR-PET (*13,14*). Contrast can also help with the detection of small bowel primaries (*15*). Given the importance of contrast-enhanced imaging studies, we strongly recommend that all SSTR-PET studies be performed with intravenous contrast whenever possible. Not only does this improve the diagnostic accuracy of the imaging study, but it also prevents the need for additional contrast-enhanced studies in the same patient.

Role of PET/MRI Versus PET/CT

PET/Magnetic Resonance Imaging is a simultaneous modality that allows for PET and MRI to be acquired together. In patients with liver-predominant NETs, this allows improved liver imaging with MRI in conjunction with SSTR-PET. Studies have shown that PET/MRI provides improved staging of liver metastases (*16,17*), but, more important, it allows for the acquisition of liver imaging with the same CI modality as used for monitoring at other times. This is important, as the imaging technique can change the appearance of liver metastases independent of their progression, and therefore a consistent imaging technique needs to be maintained across time. PET/CT, on the other

hand, is superior for patients with mesenteric, osseous, and pulmonary disease. In both PET/MRI and PET/CT, incorporation of contrast-enhanced cross-sectional imaging is encouraged.

Role of SSTR-PET in Pediatric Populations

SSTR-PET is safe in infants, children, and young adults. The dose should be adjusted to the patient's weight, and the recommended dose being 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi) (*18*). SSTR-PET is the recommended functional imaging modality for pediatric NETs and is also recommended for assessing neuroblastoma, paraganglioma, and pheochromocytoma, especially in the setting of MIBG-negative disease (*19,20*). Meningiomas occurring in children and adolescents with neurofibromatosis type 2 express SSTRs and are visualized on SSTR-PET. Pediatric indications are not addressed in the clinical scenarios.

Considerations of Tumor Grade and Imaging Modality

NETs vary in tumor aggressiveness, and tumors are categorized by histologic evaluation. Precise rules for classification vary by tumor site or origin. GEP-NETs are typically classified on the basis of the Ki67 proliferation index and/or the mitotic count (*21*) (Table 2). Well-differentiated (G1 and G2) NETs are relatively indolent, with a prognosis measured in years even in the face of metastatic disease. High-grade (G3) poorly differentiated neuroendocrine carcinomas (NECs) are typically much more aggressive and nearly always metastatic at diagnosis. Tumors in the recently identified category of well-differentiated G3 NETs are thought to harbor an intermediate prognosis (closer to traditional well-differentiated NETs) (*22*).

Unresectable well-differentiated NETs of all sites are often treated with liver-directed therapy (e.g., ablation, bland embolization, chemotherapy, or radioembolization), SSAs, or everolimus (*23,24*). Sunitinib is reserved for patients with advanced pancreatic NETs; temozolomide- or streptozocin-based chemotherapy is also typically reserved for this population (*23*). Poorly differentiated NECs (e.g., large and small cell subtypes) are typically treated with first-line platinum-based chemotherapy or with salvage therapy consisting of several other chemotherapy regimens (i.e., selected from the small cell lung carcinoma armamentarium and/or regimens commonly used for colorectal cancer if arising in the GI tract). An important consideration is that, although data from a randomized trial recently confirmed the value of peptide receptor radionuclide therapy (PRRT) in well-differentiated NETs arising in the midgut, the use of SSTR-PET is less clear in high-grade NECs.

The indications and their appropriateness reviewed in this manuscript bundle Grade 1 and Grade 2 NETs into 1 group. The exception to this may be well-differentiated Grade 3 NETs, for which optimal treatment is unclear. Patients with these tumors may be candidates for PRRT if they have high expression on SSTR-PET; SSTR-PET may therefore be helpful in selecting patients for this therapy. Typically, high-grade NECs have lower SSTR expression, as evidenced by less tracer uptake on SSTR-PET, and are better imaged with ^{18}F-FDG-PET (*25*). Furthermore, significant tumor heterogeneity can occur in patients, with the coexistence of both well-differentiated and poorly differentiated tumors; in this case, a combination of ^{18}F-FDG and SSTR-PET can be helpful in characterizing disease (*26,27*).

Understanding Stage Migration When Using SSTR-PET

Several studies indicate that SSTR-PET imaging is superior to SSTR scintigraphy or conventional anatomic imaging (CI: e.g., CT or MRI). For example, SSTR-PET can locate the primary tumor site and often demonstrates additional lesions not captured by CI, resulting in better staging that results in clinically relevant changes in management in about one-third of patients (*28*). However, it is important to recognize that identification of more 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 any other novel imaging modality, 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.

METHODOLOGY

Workgroup Selection

The experts of the AUC workgroup were convened by SNMMI to represent a multidisciplinary panel of health care providers with substantive knowledge of NETs. In addition to SNMMI member representation, international representatives from ASCO, NANETS, and EANM were included in the workgroup. Nine physician members and 1 patient advocate were ultimately selected to participate and contribute to the resulting AUC. A complete list of workgroup participants can be found in Appendix A. Appendix B is a summary of definitions of terms and acronyms, and Appendix C provides the disclosures and conflicts of interest statement.

AUC Development

The process for AUC development was modeled after the RAND/UCLA Appropriateness Method (*29,30*) and included the development of a list of common scenarios encountered in the management of patients with NETs, a systematic review of evidence related to these scenarios, and the development of an appropriateness score for each scenario by using a modified Delphi process. This process strove to adhere to the standards of the Institute of Medicine of the National Academies for developing trustworthy clinical guidance (*31*). The process included a systematic synthesis of available evidence, individual and group ratings of the scenarios by using a formal consensus process, and AUC recommendations based on final group ratings and discussions. Development of these AUC based on traditional outcome measures would have been optimal, but the literature review did not return significant numbers of articles with this information.

Scope and Development of Clinical Scenarios (or Indications)

To begin this process, the workgroup discussed various potential clinical scenarios for which the use of SSTR-PET might be considered. The scope of this workgroup was to focus on the appropriate use of SSTR-PET specifically for the

diagnosis and management of NETs. For all scenarios, the relevant populations were men and women with NETs of any age, of any race, or of any geographic location (rural, urban, etc.).

The workgroup identified 12 scenarios for patients with NETs. The scenarios are intended to be as representative of the relevant patient population as possible for development of AUC. The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each scenario. Other factors affecting the AUC recommendations were potential harm—including long-term harm that may be difficult to capture—costs, availability, and patient preferences.

Systematic Review

To inform the workgroup, a systematic review of the relevant evidence was commissioned by an independent group, the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (see Supplemental Material). The primary purpose of the systematic review was to assess the diagnostic accuracy and comparative effectiveness of SSTR-PET in patients with NETs. Two additional meta-analyses were also included in the process (*12,32*).

The key research questions used to guide the systematic review were as follows: What is the diagnostic accuracy of SSTR-PET compared with In-111 pentetreotide, ^{18}F-FDG-PET, and/or CT/MRI for identification of primary NETs, NET metastases, or tumor staging? How does diagnostic accuracy vary according to patient or tumor characteristics (e.g., Ki-67, grade and differentiation, or site of origin)? What is the predictive utility of SSTR-PET compared with OctreoScan, ^{18}F-FDG-PET, and/or CT/MRI for predicting response to PRRT or SSA therapy? How does predictive utility vary according to patient or tumor characteristics? What are the effects of SSTR-PET imaging compared with In-111 pentetreotide, ^{18}F-FDG-PET, and/or CT/MRI on clinical decision making? How do effects on clinical decision making vary according to patient or tumor characteristics?

The inclusion and exclusion criteria for papers for this review were based on the study parameters established by the workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. Searches were conducted on the following databases: the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and OVID MEDLINE (from 2000 through November 2016). These searches were supplemented by reviewing the reference lists of relevant publications.

Two reviewers independently assessed abstracts and full-text articles for inclusion and rated study quality as defined by the established PICOTS parameters. The quality (based on the risk of bias) of each study was categorized as “good,” “fair,” or “poor” by using U.S. Preventive Services Task Force criteria for randomized trials and cohort studies (*33*), Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies (*34*), and Assessment of Multiple Systematic Reviews (AMSTAR) for systematic reviews (*35*). The strength of overall evidence was graded as high, moderate, low, or very low by using methods based on quality of evidence, consistency, directness, precision, and reporting bias.

Literature searches resulted in 635 potentially relevant articles. After a dual review of the abstracts and titles, 237 articles were selected for full-text review and 17 publications were determined to meet the criteria for inclusion in this review.

Rating and Scoring Process

In developing these AUC for SSTR-PET, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: “The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics” (*36*).

At the beginning of the process, workgroup members convened at an in-person forum to develop the initial scenarios. On evaluating the evidence summary of the systematic literature review, the workgroup further refined its draft clinical scenarios to ensure their accuracy and facilitate consistent interpretation when scoring each scenario for appropriateness. Using the evidence summary, workgroup members were first asked individually to assess the benefits and risks of SSTR-PET for each of the identified scenarios and provide an appropriateness score for each scenario. After deliberate discussion, each member independently provided a second round of scores for each scenario. For each scenario, the mode numeric score was determined and then assigned to the associated appropriate use category. The results of second-round scoring continued to indicate some difference in opinion among members about the appropriateness of certain scenarios. Therefore, the workgroup continued its deliberations and further clarified the criteria for assigning the different scores before conducting a third round of scoring, which reflected a group-level consensus of scores. For this final scoring round, the members were asked to include their expert opinion. All members contributed to the final discussion, and no one was forced into consensus. After the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA Appropriateness Method.

The workgroup scored each scenario as “appropriate,” “may be appropriate,” or “rarely appropriate” on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to classify the scenario definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific scenario and generally is not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is partially arbitrary, and the numeric designations should be viewed as a continuum. In addition, if there was a difference in clinical opinion for a particular scenario such that workgroup members could not agree on a common score, that scenario was given a score of 5 to indicate a lack of agreement on appropriateness based on the available literature and the members’ collective clinical opinion, indicating the need for additional research.

CLINICAL SCENARIOS AND AUC SCORES

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.

Scenario 1: Initial staging after the histologic diagnosis of NETs (Score 9 –appropriate)

There was consensus that SSTR-PET should be used for the staging of patients with NETs. The systematic review clearly demonstrated the superiority of SSTR-PET over both CI and SSTR scintigraphy. It is important to take into account the type and size of NETs. For example, patients with subcentimeter rectal NETs likely do not require SSTR-PET at initial staging, given the extremely low incidence of metastatic disease in these patients.

Scenario 2: Localization of a primary tumor in patients with known metastatic disease, but an unknown primary (Score 9 – appropriate)

Up to 20% of patients with NETs have unknown primaries after initial workup, and localization of the primary tumor is important, as treatment options vary depending on the origin of the tumor (*37*). In one prospective study, the primary tumor was found in 38% of patients who were imaged with SSTR-PET (*38*). In another paper, the primary tumors of 4 of 14 patients with unknown primaries were detected by using SSTR-PET (*39*). This was uniformly agreed to be an appropriate indication for SSTR-PET.

Scenario 3: Selection of patients for SSTR-targeted PRRT (Score 9 – appropriate)

PRRT is increasingly becoming an important component of the treatment algorithm for patients with NETs. PRRT localizes radiation delivered by radionuclides, typically lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y), to NET cells by internalization after binding to SSTR. The pivotal prospective randomized phase 3 NETTER-1 trial demonstrated significant prolongation of progression-free survival in patients with midgut NETs after treatment with ^{177}Lu-DOTATATE compared with high-dose octreotide (*40*). For enrollment, the NETTER-1 trial did not use SSTR-PET but required patients to have evidence of SSTR expression on In-111 pentetreotide on the basis of the Krenning scale (*41*). Virtually all other single-arm PRRT studies have required uptake on SSTR imaging as an eligibility criterion. The workgroup agreed that SSTR-PET can be used in place of In-111 pentetreotide for patient selection for PRRT. Uptake on SSTR-PET can be predictive of therapeutic response to PRRT (*42*), and it is likely that SSTR-PET will prove to be a more accurate selection tool than In-111 pentetreotide for PRRT, although criteria for positive disease have yet to be developed for SSTR-PET.

Scenario 4: Staging NETs prior to planned surgery (Score 8 – appropriate)

Published series reporting on surgical cytoreduction of NET liver metastases have demonstrated that, although it is not curative, it improved survival compared with historic controls (e.g., all patients with NET metastases from large national databases) (*43–47*). The conventional wisdom is that surgical debulking “sets the clock back” but does not cure patients; thus, the presence of extrahepatic disease is not necessarily an absolute contraindication. With the development of SSTR-PET, more extensive metastatic disease is being detected, and there is no consensus on how to manage patients surgically if extensive nonresectable disease is seen on SSTR-PET. If the bulk

of metastatic disease is in the liver or abdominal lymph nodes, then surgical intervention may be warranted. In cases with extensive bone, mediastinal, and/or neck metastases, the benefits of hepatic cytoreduction are less clear, especially in those patients with impaired performance status and higher grade tumors. Nonetheless, the workgroup agreed that SSTR-PET should be used to guide surgical planning and to rule out extensive extraabdominal disease in patients prior to undergoing hepatic cytoreductive procedures.

Scenario 5: Evaluation of a mass suggestive of a NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass) (Score 8 – appropriate)

A major role for SSTR-PET is to demonstrate the presence of SSTRs noninvasively. This can help narrow the differential diagnosis of a lesion and therefore help determine the correct treatment algorithm. In the setting in which a biopsy is not easily obtained, either because of technical limitations such as the lack of access to enteroscopy or because of increased risk of invasive biopsy such as a hypervascular lesion or one too close to large vessels, SSTR-PET can demonstrate noninvasively that an uncharacterized mass is SSTR positive and therefore most likely a NET. In addition, other SSTR-positive disease may be revealed that is more amenable to biopsy.

Scenario 6: Monitoring of NETs seen predominantly on SSTR-PET (Score 8 – appropriate)

With the use of SSTR-PET, we are seeing more disease that is not appreciable on CI. In particular, osseous metastatic disease is frequently underestimated by CI (*39,48*), and the only way to visualize the extent of disease is by using SSTR-PET. In these cases, when the extent of disease cannot be reliably visualized on CI, SSTR-PET is indicated for routine imaging and follow-up.

Scenario 7: Evaluation of patients with biochemical evidence and symptoms of a NET without evidence of it on CI and without prior histologic diagnosis of a NET (Score 7 – appropriate)

This indication resulted in significant disagreement within the workgroup. On the one hand, the overall yield of finding a NET in this patient population is low, and SSTR-PET may also result in false positives that could lead to unnecessary additional tests or procedures (*12*). However, in such a situation, a negative SSTR-PET result may play an important role, as it could end the diagnostic workup, resulting in a more cost-effective evaluation. Furthermore, on the rare occasion when a study result is positive, further investigation of the lesion may be useful in identifying the tumors that are present.

Scenario 8: Restaging at time of clinical or laboratory progression without progression on CI (Score 7 – appropriate)

There was a concern that in comparison to CI, SSTR-PET may demonstrate apparent progression that would be misinterpreted and lead to inappropriate changes in management. Baseline imaging with SSTR-PET is essential, since comparison with CI would likely show more disease. Nonetheless, SSTR-PET allows better evaluation of

disease than does CI, and therefore in the setting of clinical and/or biochemical progression, it can be important for selecting the appropriate therapy.

Scenario 9: New indeterminate lesion on CI, with unclear progression (Score 7 – appropriate)

SSTR positivity is an important finding for demonstrating that a lesion is in fact a NET; therefore, to characterize a finding on CI, SSTR-PET can be used to clarify whether a suspicious lesion is a NET and represents true progression and/or recurrence. In addition, it is possible for NETs to dedifferentiate, changing from well-differentiated to poorly differentiated NETs over time (*49*). SSTR-PET can be an indirect indicator of grade, and therefore reimaging at the time of progression can provide insight into possible underlying dedifferentiation of a tumor.

Scenario 10: Restaging of patients with NETs at initial follow-up after resection with curative intent (Score 6 – may be appropriate)

There was a lack of consensus among the committee for this indication. One concern was that it would lead to overuse of SSTR-PET in patients without evidence of disease. Many suggested that a single SSTR-PET may be indicated after resection, but the main issue with the indication was the lack of impact on patient management. Visualizing small-volume residual disease after surgical resection is unlikely to change patient management; thus, some felt that it would be more appropriate to wait for biochemical evidence for recurrence or radiologic evidence on CI before performing SSTR-PET. If a patient did not undergo SSTR-PET prior to surgical resection, a single SSTR-PET should be considered to complete staging postoperatively.

Scenario 11: Selection of patients with nonfunctional NETs for SSA treatment (Score 6 – may be appropriate)

Although it is very likely that SSTR expression correlates with benefit from SSA treatment, this has not been proven definitively in clinical trials. The CLARINET trial, which demonstrated the antiproliferative activity of lanreotide in GEP-NETs, required evidence of SSTR expression with In-111 pentetreotide for enrollment (*50*). The PROMID study, which evaluated octreotide in midgut NETs, did not require evidence of SSTR expression; however, only 12% of patients had negative imaging results with In-111 pentetreotide (*51*). Only one study has reported that higher uptake on SSTR-PET predicts improved response to SSA therapy (*52*). Because of the benign side effect profile of SSAs, the workgroup did not reach a consensus that confirmation of SSTR expression is necessary for initiation of treatment with octreotide or lanreotide. The workgroup also noted that in syndromic patients, SSTR analogs should be initiated independent of findings on SSTR-PET.

Scenario 12: Monitoring in patients with NETs seen on both CI and SSTR-PET with active disease and no clinical evidence of progression (Score 5 – may be appropriate)

The consensus was that if CI can detect metastatic disease, then SSTR-PET should not be used for routine imaging. There was a belief that intermittent SSTR-PET (once every 2 to 3 years) may be helpful in evaluating for progression if CI results are stable, although it should not be used in place of CI for routine monitoring of patients.

Summary of Recommendations

SSTR-PET should replace In-111 pentetreotide in all indications in which In-111 pentetreotide is currently being used. SSTR-PET has demonstrated better sensitivity and specificity than CI and In-111 pentetreotide. There are specific instances in which SSTR-PET is clearly preferred: at initial diagnosis, when selecting patients for PRRT, and for localization of unknown primaries. For patients in which the tumor is readily seen on CI, SSTR-PET is not needed for routine monitoring.

BENEFITS AND HARMS OF IMPLEMENTING THE AUC GUIDANCE

Some providers have raised the concern that AUC for medical imaging might inappropriately limit access to health care services (*53*). For example, several authors of papers included in our meta-analysis suggested that the AUC might lead to denial of reimbursement for needed imaging services because of incomplete AUC or lack of strong evidence for a particular procedure (*54*). It is hoped that besides providing recommendations for the appropriate use of SSTR-PET, this document will demonstrate gaps in the literature and subsequently encourage new investigations to address these gaps.

Integration of AUC into clinical decision support tools can assist health care providers and offer a way to track comparisons between the AUC model and the payer's reimbursement policy (*54,55*). Ultimately, this may lead to a more efficient approval process for advanced diagnostic imaging procedures, including radiology and nuclear medicine procedures, saving time and effort for the referring provider and the imaging facility. However, the difficult task of writing AUC for all scenarios and keeping the AUC current remains a large obstacle to the effective use of the clinical decision support model.

QUALIFYING STATEMENTS

Study/Evidence Limitations

Although a large literature focuses on SSTR-PET, the workgroup found the body of medical literature regarding the use of SSTR-PET to be limited when rigorous inclusion criteria were applied to the systematic literature review. Most articles did not use pathology as a correlate to imaging and so sensitivity and specificity measurements were often limited. Information was also scarce on the role of SSTR-PET in high-grade NECs and other less common subtypes of NETs (e.g., well-differentiated G3 NETs, paraganglioma/pheochromocytoma). In addition, little data were available on the use of SSTR-PET in pediatric populations or on how SSTR-PET can be used to predict and evaluate the response to PRRT.

IMPLEMENTATION OF THIS AUC GUIDANCE

SNMMI has been working with several other medical specialty societies to develop broad-based multidisciplinary clinical guidance documents. This collaboration should foster the acceptance and adoption of this guidance by other specialties.

SNMMI has developed a multipronged approach to disseminate the AUC for SSTR-PET in NETs to all relevant stakeholders—referring physicians, nuclear medicine

physicians, and patients. The dissemination and implementation tactics will be a mix of outreach and educational activities and will be targeted to each of these audiences.

SNMMI will create detailed case studies for its members and for referring physicians and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of SSRT-PET, as well as some cases in which the results of SSRT-PET are equivocal.

Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on the AUC, factsheets, and other didactic materials will be made available on the SNMMI webpage dedicated to the SSRT-PET AUC. Live sessions will be held at the SNMMI annual and midwinter meetings, as well as at the relevant societal meetings of referring physicians, to highlight the importance of these AUC.

SNMMI also aims to create a mobile application for the SSTR-PET AUC for both Apple and Android platforms. Mobile applications are becoming increasingly popular in the health-care industry and can be used to push updates to all users.

In addition to these activities, SNMMI will undertake patient-focused outreach to provide education on how AUC can play an invaluable role in achieving a more accurate diagnosis.

REFERENCES

1. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121:589–597.

2. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017.

3. John M, Meyerhof W, Richter D, et al. Positive somatostatin receptor scintigraphy correlates with the presence of somatostatin receptor subtype 2. *Gut*. 1996;38:33–39.

4. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med*. 1993;20:716–731.

5. Bombardieri E, Ambrosini V, Aktolun C, et al. 111In-pentetreotide scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging*. 2010;37:1441–1448.

6. Lamberts SW, Bakker WH, Reubi JC, Krenning EP. Somatostatin-receptor imaging in the localization of endocrine tumors. *N Engl J Med*. 1990;323:1246–1249.

7. Antunes P, Ginj M, Zhang H, et al. Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? *Eur J Nucl Med Mol Imaging*. 2007;34:982–993.

8. Poeppel TD, Binse I, Petersenn S, et al. 68Ga-DOTATOC versus 68Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med*. 2011;52:1864–1870.

9. Velikyan I, Sundin A, Sörensen J, et al. Quantitative and qualitative intrapatient comparison of 68Ga-DOTATOC and 68Ga-DOTATATE: net uptake rate for accurate quantification. *J Nucl Med*. 2014;55:204–210.

10. Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of 68Ga-DOTATATE. *J Nucl Med*. 2013;54:855–860.

11. Hartmann H, Zöphel K, Freudenberg R, et al. [Radiation exposure of patients during 68Ga-DOTATOC PET/CT examinations]. *Nuklearmedizin*. 2009;48:201–207.

12. Graham MM, Gu X, Ginader T, Breheny P, Sunderland J. (68)Ga-DOTATOC imaging of neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl*

Med. 2017.

13. Badiee S, Franc BL, Webb EM, et al. Role of IV iodinated contrast material in 18F-FDG PET/CT of liver metastases. *American Journal of Roentgenology*. 2008;191:1436–1439.

14. Ruf J, Heuck F, Schiefer J, et al. Impact of Multiphase 68Ga-DOTATOC-PET/CT on therapy management in patients with neuroendocrine tumors. *Neuroendocrinology*. 2010;91:101–109.

15. Schreiter NF, Maurer M, Pape U-F, Hamm B, Brenner W, Froeling V. Detection of neuroendocrine tumours in the small intestines using contrast-enhanced multiphase Ga-68 DOTATOC PET/CT: the potential role of arterial hyperperfusion. *Radiol Oncol*. 2014;48:120–126.

16. Hope TA, Pampaloni MH, Nakakura E, et al. Simultaneous (68)Ga-DOTA-TOC PET/MRI with gadoxetate disodium in patients with neuroendocrine tumor. *Abdom Imaging*. 2015;40:1432–1440.

17. Sawicki LM, Deuschl C, Beiderwellen K, et al. Evaluation of (68)Ga-DOTATOC PET/MRI for whole-body staging of neuroendocrine tumours in comparison with (68)Ga-DOTATOC PET/CT. *European radiology*. 2017;26:3063–3069.

18. NETSPOT Prescribing Information. www.accessdata.fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208547s000lbl.pdf. Accessed April 8, 2017.

19. Kong G, Hofman MS, Murray WK, et al. Initial experience with gallium-68 DOTA-octreotate PET/CT and peptide receptor radionuclide therapy for pediatric patients with refractory metastatic neuroblastoma. *J Pediatr Hematol Oncol*. 2016;38:87–96.

20. Kroiss A, Putzer D, Uprimny C, et al. Functional imaging in phaeochromocytoma and neuroblastoma with 68Ga-DOTA-Tyr 3-octreotide positron emission tomography and 123I-metaiodobenzylguanidine. *Eur J Nucl Med Mol Imaging*. 2011;38:865–873.

21. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010;39:707–712.

22. Raj N, Valentino E, Capanu M, et al. Treatment response and outcomes of grade 3 pancreatic neuroendocrine neoplasms based on morphology: well differentiated versus poorly differentiated. *Pancreas*. 2017;46:296–301.

23. Raymond E, Dahan L, Raoul J-L, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:501–513.

24. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387:968–977.

25. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. *Cancer*. 2008;112:2447–2455.

26. Hofman MS, Hicks RJ. Changing paradigms with molecular imaging of neuroendocrine tumors. *Discov Med*. 2012;14:71–81.

27. Chan DL, Pavlakis N, Schembri GP, et al. Dual somatostatin receptor/FDG PET/CT imaging in metastatic neuroendocrine tumours: proposal for a novel grading scheme with prognostic significance. *Theranostics*. 2017;7:1149–1158.

28. Barrio M, Czernin J, Fanti S, et al. The impact of somatostatin receptor-directed PET/CT on the management of patients with neuroendocrine tumor: a systematic review and meta-analysis. *J Nucl Med*. 2017;58:756–761.

29. Hendel RC, Patel MR, Allen JM, et al. Appropriate use of cardiovascular technology: 2013 ACCF appropriate use criteria methodology update: a report of the American College of Cardiology Foundation appropriate use criteria task force. *J Am Coll Cardiol*. 2013;61:1305–1317.

30. Fitch K, Bernstein SJ, Aguilar MD, Burnand B. The RAND/UCLA appropriateness method user's manual. Santa Monica, CA: RAND; 2001.

31. Institute of Medicine of the National Academy. Clinical practice guidelines we can trust. National Academies Press. Washington, DC: National Academy of Sciences; 2011.

32. Deppen SA, Blume J, Bobbey AJ, et al. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl Med*. 2016;57:872–878.

33. US Preventive Services Task Force. US preventive services task force procedure manual. Rockville, MD: Agency for Healthcare Research and Quality. 2008.

34. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155:529–536.

35. Shea BJ, Bouter LM, Peterson J, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). Gagnier J, editor. *PLoS ONE*. 2007;2:e1350–e1355.

36. Appropriate use criteria (AUC) development process. snmmi.org.

http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=15665. Accessed August 5, 2017.

37. Bellizzi AM. Assigning site of origin in metastatic neuroendocrine neoplasms: a clinically significant application of diagnostic immunohistochemistry. *Adv Anat Pathol*. 2013;20:285–314.

38. Menda Y, O'Dorisio TM, Howe JR, et al. Localization of unknown primary site with (68)Ga-DOTATOC PET/CT in patients with metastatic neuroendocrine tumor. *J Nucl Med*. 2017;58:1054–1057.

39. Sadowski SM, Neychev V, Millo C, et al. Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol*. 2016;34:588–596.

40. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125–135.

41. Krenning EP, Valkema R, Kooij PP, et al. Scintigraphy and radionuclide therapy with [indium-111-labelled-diethyl triamine penta-acetic acid-D-Phe1]-octreotide. *Ital J Gastroenterol Hepatol*. 1999;31 Suppl 2:S219–S223.

42. Kratochwil C, Stefanova M, Mavriopoulou E, et al. SUV of [(68)Ga]DOTATOC-PET/CT predicts response probability of PRRT in neuroendocrine tumors. *Mol Imaging Biol*. 2015;17(3):313-8.

43. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg*. 2003;197:29–37.

44. Glazer ES, Tseng JF, Al-Refaie W, et al. Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB (Oxford)*. 2010;12:427–433.

45. Mayo SC, de Jong MC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol*. 2010;17:3129–3136.

46. Graff-Baker AN, Sauer DA, Pommier SJ, Pommier RF. Expanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients. *Surgery*. 2014;156:1369–76–discussion1376–7.

47. Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? *Surgery*. 2016;159:320–333.

48. Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with

neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. *J Nucl Med*. 2009;50:1214–1221.

49. Tang LH, Untch BR, Reidy DL, et al. Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. *Clin Cancer Res*. 2016;22:1011–1017.

50. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371:224–233.

51. Rinke A, Müller H-H, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27:4656–4663.

52. Koch W, Auernhammer CJ, Geisler J, et al. Treatment with octreotide in patients with well-differentiated neuroendocrine tumors of the ileum: prognostic stratification with Ga-68-DOTA-TATE positron emission tomography. *Mol Imaging*. 2014;13:1–10.

53. Bettmann MA. The ACR Appropriateness Criteria: view from the committee chair. *J Am Coll Radiol*. 2006;3:510–512.

54. Thrall JH. Appropriateness and imaging utilization: "computerized provider order entry and decision support". *Acad Radiol*. 2014;21:1083–1087.

55. Sistrom CL. In support of the ACR appropriateness criteria. *J Am Coll Radiol*. 2008. pp. 630–5–discussion636–7.

56. Brix G, Lechel U, Glatting G, et al. Radiation exposure of patients undergoing whole-body dual-modality 18F-FDG PET/CT examinations. *J Nucl Med*. 2005;46:608–613.

TABLE 1
Dosimetry for ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC

	^{68}Ga-DOTATATE (***10***)	^{68}Ga-DOTATOC (***11***)	^{18}F-FDG (***56***)
Organ			
Kidneys (mSv/MBq)	9.2E-02	2.2E-01	1.7E-02
Liver (mSv/MBq)	4.5E-02	7.4E-02	2.1E-02
Spleen (mSv/MBq)	2.8E-01	2.4E-01	1.1E-02
Bladder wall (mSv/MBq)	1.3E-01	7.0E-02	1.3E-01
Dose			
ED (mSv/MBq)	2.6E-02	2.3E-02	1.9E-02
Typical injected activity			
MBq	185	185	370
mCi	5	5	10
Estimated effective dose per scan (mSv)	4.8	4.3	7.0

TABLE 2
Classification of GEP-NETs (*21*)

Differentiation	Grade	Ki67 index	Proliferative rate	SSTR-PET positivity
Well differentiated	Low grade (G1)	<3%	<2 mitoses/10 hpf	+++
	Intermediate grade (G2)	3%–20%	2–20 mitoses/10 hpf	++
Poorly differentiated	High grade (G3)	>20%	>20 mitoses/20 hpf	Variable*

GEP-NETs = gastroenteropancreatic-neuroendocrine tumors; SSTR-PET = somatostatin receptor positron emission tomography.
*In high-grade NETs, SSTR positivity is variable, and frequently ^{18}F-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 peptide receptor radionuclide therapy.

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 a primary tumor in patients with known metastatic disease but an unknown primary	Appropriate	9
3	Selection of patients for SSTR-targeted PRRT	Appropriate	9
4	Staging NETs prior to planned surgery	Appropriate	8
5	Evaluation of a mass suggestive of a NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass)	Appropriate	8
6	Monitoring of NETs seen predominantly on SSTR-PET	Appropriate	8
7	Evaluation of patients with biochemical evidence and symptoms of a NET without evidence of it on CI and without prior histologic diagnosis of a NET	Appropriate	7
8	Restaging at time of clinical or laboratory progression without progression on CI	Appropriate	7
9	New indeterminate lesion on CI with unclear progression	Appropriate	7
10	Restaging of patients with NETs at initial follow-up after resection with curative intent	May be appropriate	6
11	Selection of patients with nonfunctional NETs for SSA treatment	May be appropriate	6
12	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

SSTR-PET = somatostatin receptor positron emission tomography; NET = neuroendocrine tumor; PRRT = peptide receptor radionuclide therapy; CI = conventional imaging; SSA = somatostatin analog.

Appendix A: Workgroup members and literature reviewers

Workgroup members: Thomas A. Hope, MD (chair), University of California, San Francisco, San Francisco, CA (SNMMI/ACR); Emily K. Bergsland, MD, University of California, San Francisco, San Francisco, CA (ASCO/NANETS); Murat Fani Bozkurt, MD, Hacettepe University, Ankara, Turkey (EANM); Michael Graham, PhD, MD, University of Iowa, Iowa City, IA (SNMMI); Anthony P. Heaney, MD, University of California, Los Angeles, Los Angeles, CA (Endocrine Society); Ken Herrmann, MD, Universitatsklinikum Essen, Essen, Germany (EANM); James R. Howe, MD, University of Iowa, Iowa City, IA (Society of Surgical Oncology/NANETS); Matthew H. Kulke, MD, Dana-Farber Cancer Institute, Boston, MA (ASCO/NANETS/NCCN); Pamela Kunz, MD, Stanford University, Stanford, CA (ASCO/NANETS); Josh Mailman, President, NorCal Carcinet (patient advocate); Lawrence May, MD, Los Angeles, CA (ACP); David C. Metz, MD, University of Pennsylvania, Philadelphia, PA (AGA/NANETS); Corina Millo, MD, National Institutes of Health, Bethesda, MD (SNMMI); Sue O'Dorisio, MD, PhD, University of Iowa, Iowa City, IA (SNMMI/ASCO/NANETS); Diane L. Reidy-Lagunes, MD, Memorial Sloan Kettering Cancer Center, New York, NY (ASCO/NANETS); Michael C. Soulen, MD, University of Pennsylvania, Philadelphia, PA (NANETS, WCIO); Jonathan R. Strosberg, MD, Moffitt Cancer Center, Tampa, FL (ASCO, NANETS).

Literature reviewers: Roger Chou, MD, Oregon Health Sciences University, Portland, OR; Elaine Graham, Oregon Health Sciences University, Portland, OR; Miranda Pappas, Oregon Health Sciences University, Portland, OR; Barbara Ray, Oregon Health Sciences University, Portland, OR.

SNMMI staff support: Sukhjeet Ahuja, MD, MPH, Director, Evidence & Quality Department; Julie Kauffman, Program Manager, Evidence & Quality Department; Bonnie Clarke, Director, Clinical Trials Network.

Appendix B: Definition of Terms and Acronyms

ACP: American College of Physicians
ACR: American College of Radiology
AGA: American Gastroenterological Association
ASCO: American Society of Clinical Oncology
AUC: appropriate use criteria
CI: conventional imaging (CT, MRI, ultrasound, plain film radiography)
CT: A computed tomography (CT) scan is an imaging method that uses x-rays to create pictures of cross-sections of the body.
EANM: European Association of Nuclear Medicine
GEP: gastroenteropancreatic
MRI: magnetic resonance imaging
NANETS: North American Neuroendocrine Tumor Society
NCCN: National Comprehensive Cancer Network
NEC: neuroendocrine carcinoma
NET: neuroendocrine tumor
OctreoScan: ^{111}In-pentetreotide scintigraphy
PET: positron emission tomography
PET/CT: A combination device that provides detail on both function and anatomy by superimposing the precise location of abnormal metabolic activity (from PET) on a detailed anatomic image (from CT).
PRRT: peptide receptor radionuclide therapy
SNMMI: Society of Nuclear Medicine and Molecular Imaging
SSA: somatostatin analog
SSTR: somatostatin receptor
SSTR-PET: somatostatin receptor positron emission tomography
WCIO: World Conference on Interventional Oncology

Appendix C: Disclosures and Conflicts of Interests (COIs)

SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures of the workgroup members can be found in Table 1C. A COI was defined as a relationship with industry—including consulting, speaking, research, and nonresearch activities—that exceeds $5,000 in funding over the previous or upcoming 12-month period. In addition, if an external reviewer was either the principal investigator of a study or another key member of the study personnel, that person's participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of this AUC document. All external reviewers were asked about any potential COI.

Evidence Synthesis_ - Rapid Review

Systematic Review: Somatostatin Imaging for Neuroendocrine Tumors

Prepared for:
The Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive
Reston, VA 20190-5316
www.snmmi.org

Prepared by:
Pacific Northwest Evidence-based Practice Center
Oregon Health & Science University
Mail Code: BICC
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Roger Chou, MD
Miranda Pappas, MA
Liev Miller, BA

May 2017

Acknowledgements

The authors acknowledge Andrew Hamilton, MLS, MS, for conducting literature searches at the Oregon Health & Science University.

ABSTRACT

Background. Somatostatin receptor-positron emission tomography (SSTR-PET) is a functional imaging technique used to identify neuroendocrine tumors. The purpose of this report is to assess the comparative diagnostic accuracy of ^{68}Ga-DOTATOC (gallium-68 1, 4, 7, 10-tetraazocyclodecane-1, 4, 7, 10-tetraacetic acid edotreotide) or ^{68}Ga-DOTATATE (gallium-68 1, 4, 7, 10-tetraazocyclodecane-1, 4, 7, 10-tetraacetic acid (Tyr^3)-octreotate) positron emission tomography (PET) versus functional imaging with octreotide coupled with radiolabeled indium-111 and the chelator diethylenetriaminepentacetic acid (^{111}In-DTPA SPECT, referred to by the trade name OctreoScan®), 18 fludeoxyglucose-fluor-2-deoxy-D-glucose (^{18}FDG)-PET, or anatomical imaging with magnetic resonance imaging (MRI) or computed tomography (CT) for detecting neuroendocrine tumors (NETs), comparative predictive utility for predicting response to treatment with somatostatin analogues or peptide receptor radionuclide therapy (PRRT), and effects on clinical decision-making.

Data Sources. Searches were conducted on the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE® (through November 2016); studies were also identified from reference lists.

Review Methods. We selected studies of the diagnostic accuracy of ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET (with or without CT) versus OctreoScan or MRI/CT for identification of NETs, based on a a reference standard consisting of histopathology or histopathology and clinical/imaging follow-up. We also included studies on effects of the utility of SSTR-PET versus alternative imaging for predicting response to somatostatin analogue therapy or PRRT,

and effects of SSTR-PET on clinical decision-making. Two reviewers independently assessed studies for inclusion and rated study quality. One reviewer abstracted data and a second checked it. Strength of evidence was assessed using GRADE methods.

Results. Fifteen diagnostic accuracy studies and seven studies on clinical decision-making met inclusion criteria. SSTR-PET was associated with greater sensitivity than OctreoScan (difference in sensitivity ranged from 14% to 56%) and ^{18}FDG-PET (difference in sensitivity ranged from 24% to 75%) for diagnosis of NETs. Findings were generally consistent for diagnosis of pulmonary NETs, gastroenteropancreatic (GEP) NETs, or both, as well as for primary and metastatic lesions. SSTR-PET was also associated with higher sensitivity for identification of primary NET than CT/MRI (differences in sensitivity ranged from 12% to 49%). For metastatic lesions, three studies reported inconsistent findings between SSTR-PET and MRI. Most studies reported no clear differences in specificity between SSTR-PET and alternative imaging modalities. Evidence on how comparative diagnostic accuracy varies according to tumor or patient characteristics is limited.

No study compared the utility of SSTR-PET with alternative imaging modalities for predicting response to PRRT or somatostatin analogue therapy. Two noncomparative studies of SSTR-PET found the degree of radiotracer uptake associated with the likelihood of treatment response, diagnostic accuracy was suboptimal.

Five studies found that SSTR-PET was associated with changes in management in 13% to 60% of patients, but the studies had important methodological limitations.

Conclusions. SSTR-PET is associated with higher sensitivity than OctreoScan and ^{18F}DG-PET for identification of primary and metastatic NETs, and higher sensitivity than MRI or CT for

identification of primary NETs. Research is needed to clarify the utility of SSTR-PET for predicting response to somatostatin therapy or PRRT and effects on clinical-decision-making.

Table of Contents

Introduction.....1
Methods.....4
Key Questions.....4
Search Strategies.....5
Study Selection.....5
Data Abstraction.....6
Assessing Methodological Quality of Individual Studies.....6
Synthesizing the Evidence and Grading the Strength of Evidence.....8
Results.....9
Results of Literature Searches.....10
Key Question 1. What is the diagnostic accuracy of SSTR-PET compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI for identification of primary NET, NET metastasis, or for tumor staging?.....10
Key Question 1a. How does diagnostic accuracy vary according to patient or tumor characteristics (e.g., Ki-67, grade and differentiation, or site of origin)?.....16
Key question 2. What is the predictive utility of SSTR-PET compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI for predicting response to PRRT or somatostatin analogue therapy?.....17
Key Question 2a. How does predictive utility vary according to patient or tumor characteristics?.....18
Key Question 3. What are the effects of SSTR-PET imaging compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI on clinical decision-making?.....18
Key Question 3a. How do effects on clinical decision-making vary according to patient or tumor characteristics?.....19
Discussion.....20
References.....23

Appendixes
Appendix 1. Table of Systematic Reviews
Appendix 2. Search Strategies
Appendix 3. Literature Flow Diagram
Appendix 4. Evidence Tables
Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs
Table 4b. Summarized Characteristics of Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs
Table 4c. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs
Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs
Appendix 5. Quality Assessment Criteria
Appendix 6. Quality Assessment Tables
Table 6a. Quality Assessments of Studies of Diagnostic Accuracy
Table 6b. Quality Assessment of Cohort Studies
Appendix 7. Strength of Evidence Table

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that originate from various types of neuroendocrine cells.[1-3] NETs are rare, accounting for approximately 1.5% of all gastrointestinal and pancreatic neoplasms. NETs most commonly occur in the gastrointestinal tract, lungs, and pancreas, but can occur in other areas of the body (e.g., thyroid, brain). NETs can be classified broadly as those that exhibit more indolent behavior and those with an aggressive course. Indolent NETs are characterized by slow growth and progression to metastasize, and they are often associated with secretion of hormones or vasoactive substances. NETs with indolent biology include carcinoid tumors (gastrointestinal or bronchial well-differentiated neuroendocrine carcinomas), pancreatic NETs (e.g., insulinoma, gastrinoma, glucagonoma, somatostatinoma, VIPoma, or nonfunctioning pancreatic NETs), medullary thyroid cancers, and pheochromocytoma. Aggressive NETs often present at advanced stages and have a high propensity to metastasize; these tumors are generally poorly differentiated and less likely to secrete hormones or vasoactive substances. NETs with aggressive biology include small cell and large cell neuroendocrine lung cancer, high-grade poorly differentiated neuroendocrine carcinoma, extrapulmonary small cell carcinoma, Merkel cell tumor of the skin, and neuroblastoma. NETs may also present as metastatic disease with an unknown primary site.

Imaging of NETs is required for accurate diagnosis and staging, which is critical for guiding therapy (e.g., suitability for surgical resection or radionuclide therapy for surgically unresectable tumors).[4] NETs are characterized by high density and expression of somatostatin receptors, which can be targeted by radiolabeled peptide analogues of somatostatin and visualized using various imaging techniques.[5-7] Unlike traditional imaging based solely on anatomic findings (e.g., computed tomography [CT] or magnetic resonance imaging [MRI]), the

use of radionuclide images is also based on the physiological and functional characteristics of the tumor, which may help in detection of small or otherwise difficult to visualize tumors and increase specificity compared with anatomic imaging.[8]

Octreotide coupled with radiolabeled indium-111 and the chelator diethylenetriaminepentacetic acid (^{111}In-DTPA, also referred to as ^{111}In-pentetreotide), has been the most widely used somatostatin analogue for functional imaging of NETs.[9] Visualization is performed with single-photon emission computed tomography (SPECT) scintigraphy; this imaging technique is commonly referred to by the trade name OctreoScan®. SPECT images may be fused with CT to increase resolution (SPECT/CT). However, even when coupled with CT, OctreoScan is associated with limited spatial resolution and relatively low image quality; other shortcomings include the need for a prolonged imaging protocol and relatively high radiation dose.[10]

More recently, positron emission tomography (PET) imaging utilizing octreotide derivatives such as (Tyr^3)-octreotate (TATE) and edotreotide (TOC), coupled with positron emitting isotopes such as gallium-68 (^{68}Ga) and the chelator 1, 4, 7, 10-tetraazocyclodecane-1, 4, 7, 10-tetraacetic acid (DOTA) have been introduced.[11,12] Compared with OctreoScan, PET imaging with ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC (referred to in this report as somatostatin receptor PET imaging, or SSTR-PET) is associated with increased spatial resolution and lesion detectability, potentially resulting in greater accuracy for diagnosis and staging. One recent systematic review of 22 studies found SSTR-PET or PET/CT with primarily ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC (18 studies) associated with high pooled sensitivity (93%, 95% confidence interval [CI] 91% to 94%) and specificity (96%, 95% CI 95% to 98%), with an area under the receiver operating curve (AUROC) of 0.98 (95% CI 0.95 to 1.0)[13] (**Appendix 1**). Another

systematic review of 10 studies found SSTR-PET or PET/CT with ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC associated with similar accuracy (pooled sensitivity 93% vs. 96%, respectively; pooled specificity 85% vs. 100%; AUROC 0.96 vs. 0.98).[14] Other advantages include shorter imaging time (<2 hours vs. 2 days for OctreoScan) and lower radiation exposure.

The purpose of this rapid systematic review is to synthesize the evidence on the comparative performance of SSTR with ^{68}Ga-DOTA peptide (DOTATATE and DOTATOC) versus imaging with OctreoScan, fludeoxyglucose 18 (^{18}FDG)-PET, or anatomic imaging with MRI/CT on diagnostic accuracy for NETs, accuracy for predicting response to treatment with somatostatin analogues or peptide receptor radionuclide therapy (PRRT), and comparative effects on clinical decision-making.

METHODS

Key Questions

In conjunction with an Appropriate Use Criteria (AUC) Workgroup convened by the Society of Nuclear Medicine and Molecular Imaging, we determined the scope and clinical questions for this review on SSTR for detection of NETs. The AUC Workgroup selected the NET types to focus on for this review.

Key Questions:

1. What is the diagnostic accuracy of SSTR-PET compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI for identification of primary NET, NET metastasis, or for tumor staging?
    a. How does diagnostic accuracy vary according to patient or tumor characteristics (e.g., Ki-67, grade and differentiation, or site of origin)?
2. What is the predictive utility of SSTR-PET compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI for predicting response to PRRT or somatostatin analogue therapy?
    a. How does predictive utility vary according to patient or tumor characteristics?
3. What are the effects of SSTR-PET imaging compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI on clinical decision-making?
    a. How do effects on clinical decision-making vary according to patient or tumor characteristics?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE® (1996 to November 2016) for relevant studies and systematic reviews. Search strategies are shown in **Appendix 2**. We supplemented searches of electronic databases with a review of reference lists of relevant articles.

Study Selection

Two investigators independently reviewed abstracts and full-text articles against pre-specified eligibility criteria, as defined by the Population, Interventions, Comparisons, Outcomes, Timing, and Setting (PICOTS). We included studies of patients undergoing imaging with PET with or without CT using somatostatin receptor tracers (either ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC) for suspicion of or confirmation of NETs compared with alternative imaging (CT alone, MRI, ^{18}F-FDG PET, or OctreoScan). We included studies that reported the diagnostic accuracy of ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET for detection of NETs. We included studies that compared ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET against a reference standard consisting of histopathology; studies that did not use a histopathologic reference standard in all patients had to utilize both clinical and imaging follow-up to be included in our review. Studies could also compare ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET against another imaging modality. We excluded studies that did not use an alternative imaging modality from the index test in the reference standard. We also included studies that compared the predictive utility of SSTR-PET imaging versus the imaging modalities described above for identifying responders to PRRT or somatostatin analogue therapy.

For studies on effects of ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET on clinical decision-making and clinical outcomes, we selected studies that compared effects of ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC PET versus no ^{68}Ga-DOTA peptide imaging or an alternative imaging modality in patients with NETs and reported effects on treatment decisions or clinical outcomes (e.g., mortality, morbidity, quality of life, and harms).

We excluded non-English language articles and studies published only as conference abstracts. The selection of literature is summarized in the literature flow diagram (**Appendix 3**).

Data Abstraction

We extracted the following data from primary studies: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, imaging characteristics, and results. All study data were abstracted by one investigator and verified for accuracy and completeness by a second team member. See **Appendix 4** for evidence tables with extracted data.

Assessing Methodological Quality of Individual Studies

Two investigators independently assessed the quality (risk of bias) of each study as "good," "fair," or "poor" using pre-defined criteria specific for each study design. Specifically, we used AMSTAR (Assessing the Methodological Quality of Systematic Reviews) for systematic reviews,[15-17] U.S. Preventive Services Task Force criteria[18] for randomized trials and cohort studies, and QUADAS-2[19] (Quality Assessment of Diagnostic Accuracy Studies-2) for studies of diagnostic accuracy (**Appendix 5**). Discrepancies were resolved through a consensus process.

Studies rated “good” are considered to have the least risk of bias and their results are generally considered valid. Good-quality systematic reviews perform comprehensive and reproducible searches and results, use pre-defined criteria for selection of studies, evaluate the quality of included studies and incorporate assessments of quality when synthesizing data, use appropriate methods for synthesizing data, and have conclusions supported by the evidence. Good-quality studies of diagnostic accuracy avoid bias in the selection of patients (e.g., enrolling consecutive patients meeting inclusion criteria or a random sample and avoiding a case-control design), perform interpretation of the reference standard blinded to the results of the imaging test and vice versa, use a valid reference standard in all patients, use pre-defined criteria to define a positive imaging test, and include all patients in the analysis. Good-quality intervention studies use valid methods to select patients for inclusion and allocate patients to treatment, report similar baseline characteristics in different treatment groups, clearly report attrition and have low attrition; use appropriate methods to reduce performance bias (e.g., blinding of patients, care providers, and outcome assessors), and use appropriate analytic methods (e.g., intention-to-treat analysis).

Studies rated “fair” are susceptible to some bias, though not enough to necessarily invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may also be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting. The

results of poor-quality studies are at least as likely to reflect flaws in the study design as the true difference between the compared interventions. We rated diagnostic accuracy studies that only reported sensitivity but not specificity as poor-quality since they provide incomplete diagnostic accuracy information; we also rated studies with significant data discrepancies (e.g., reported sensitivity/specificity do not match the raw 2 x 2 numbers provided in the study) as poor-quality. We did not exclude studies rated poor-quality *a priori*, but such studies were considered to be less reliable than higher-quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

For further details about the quality of included studies and reviews see tables in **Appendix 6**.

Synthesizing the Evidence and Grading the Strength of Evidence

We did not perform a meta-analysis on studies of diagnostic accuracy because the studies used different methods to assess accuracy, had heterogeneity in terms of the types of NETs evaluated, and there were methodological limitations in the studies. Instead, we synthesized the evidence qualitatively. For studies of diagnostic accuracy, we constructed 2 x 2 tables and calculated sensitivity and specificity with associated 95% CIs. If we could not construct a 2 x 2 table we relied on the diagnostic accuracy estimates as reported in the study. We constructed 2 x 2 tables using a "per-patient" approach when the data were available (i.e., patients with or without NETs), and used a "per-lesion" approach (one patient could have multiple lesions) when per-patient data were not available.

We assessed the strength of evidence for each key question, type of NET, and outcome based on the overall quality of each body of evidence (graded good, fair, or poor); the consistency of results across studies (graded consistent, inconsistent, or unable to determine when only one study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); the precision of the estimate of effect, based on the number and size of studies and CI for the estimates (graded precise or imprecise); and reporting bias (suspected of undetected),[20,21] using methods adapted for studies of diagnostic accuracy.[22,23] We graded comparisons and outcomes imprecise if there were fewer than 100 total patients or if the studies reported a less than 20% difference in sensitivity or specificity between the lower and upper limits of the CI. We did not downgrade studies on diagnostic accuracy for assessing intermediate outcomes, since the key questions were specified for diagnostic accuracy.

We graded the strength of evidence for each key question using four key categories.[21] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

See **Appendix 7** for the strength of evidence table.

RESULTS

Results of Literature Searches

The search and selection of articles are summarized in the literature flow diagram (**Appendix 3**). Database searches resulted in 635 potentially relevant articles. After dual review of abstracts and titles, 237 articles were selected for full-text dual review and 17 studies were determined to meet inclusion criteria and were included in this review. Data extraction and quality assessment tables for all included studies are available in tables in **Appendixes 4 and 6**.

Key Question 1. What is the diagnostic accuracy of SSTR-PET compared with OctreoScan, 18FDG-PET, and/or CT/MRI for identification of primary NET, NET metastasis, or for tumor staging?

Fifteen studies compared the diagnostic accuracy of SSTR-PET with OctreoScan, ^{18}FDG-PET or CT/MRI (**Table 4a and 4b**).[24-38] Sample sizes ranged from 18 to 131; the total number of patients across all studies was 679. Two studies were conducted in the United States, nine in Europe, and four elsewhere. Five studies compared SSTR-PET with OctreoScan, four studies compared SSTR-PET with ^{18}FDG-PET, and ten studies compared SSTR-PET with CT or MRI. Four studies used ^{68}Ga-DOTATATE and ten used ^{68}GaDOTATOC; one study used ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, or ^{68}Ga–DOTANOC.[30] Four studies evaluated accuracy for detection of various NETs (primarily gastroenteropancreatic [39] or pulmonary NETs),[24-27] four studies on accuracy for detection of GEP NETs,[28,29,31,38] two studies on accuracy for detection of pulmonary NETs,[30,37] five studies on accuracy for detection of metastatic disease due to NETs,[29,32,34-36] and one study on detection of unknown primary or metastatic NETs.[33] The

reference standards varied across studies (**Table 4b**). Four studies required histological confirmation;[29,30,37] in the other studies the reference standard consisted of various combinations of follow-up imaging, clinical follow-up, and histological confirmation. Eight studies analyzed diagnostic accuracy on a per-patient basis;[24,27,29,30,32,34,37,38] the remainder only reported accuracy on a per-lesion basis.

Two studies were rated good-quality,[27,37] eight studies fair-quality,[24-26,31,32,34,35,38] and five studies[28-30,33,36] poor-quality (**Table 6a**). Frequent methodological shortcomings in the fair- and poor-quality studies were unclear methods for selection of patients, use of a case-control design, and failure to report independent interpretation of the reference standard from the imaging test. In one poor-quality study,[29] there were significant discrepancies between the data reported and results. In five poor-quality studies, specificity was not reported and could not be calculated.[28,30,33,34,36]

SSTR-PET Compared With OctreoScan

Five studies compared diagnostic accuracy of SSTR-PET with OctreoScan (**Table 4c**).[24,25,31,33,36] Two studies evaluated accuracy for detection of NETs (primarily GEP or pulmonary),[24,25] one study evaluated accuracy for detection of duodenopancreatic NETs,[31] one study evaluated accuracy for detection of unknown primary or metastatic NETs,[33] and one study evaluated accuracy for detection of metastatic disease.[36] All reported per-lesion analyses. In all studies, SSTR-PET was associated with higher sensitivity for detecting NETs than OctreoScan.

For identification of GEP or pulmonary NETs, one fair-quality study (n=50) found SSTR-PET/CT with ^{68}Ga-DOTATOC associated with higher sensitivity than OctreoScan (97% vs. 83%, McNemar's p=0.01).[24] Another fair-quality study (n=19) found SSTR-PET/CT with

^{68}Ga-DOTATATE associated with higher sensitivity for detection of primary or metastatic NETs than OctreoScan (96% vs. 60%, McNemar's p=0.03).[25] In both studies, specificity was high (≥95%) and similar for both SSTR-PET/CT and OctreoScan.

For diagnosis of GEP NETs in patients with multiple endocrine neoplasia (MEN) syndrome type 1, one fair-quality study (n=19) found ^{68}Ga-DOTATOC PET/CT associated with higher sensitivity than OctreoScan (76% vs. 20%, p<0.0001 for comparison of SSTR-PET/CT, OctreoScan, and CT).[31] SSTR-PET/CT was also associated with higher specificity (100% vs. 50%, p<0.01).

For diagnosis of unknown primary or metastatic NETs, one poor-quality study (n=131) found ^{68}Ga-DOTATATE PET/CT associated with higher sensitivity for identification of unknown primary or metastatic NETS than OctreoScan (95% vs. 31%, p<0.001).[33] Another poor-quality study (n=53) found ^{68}Ga-DOTATOC PET/CT associated with higher sensitivity than OctreoScan (SPECT/CT) for detection of metastatic NET lesions (99.9% vs. 60%, p<0.01).[36]

SSTR-PET Compared With ^{18}FDG-PET

Four studies (n=20 to 32) compared the diagnostic accuracy of SSTR-PET/CT with ^{18}FDG-PET (**Table 4c**).[28-30,37] One study evaluated accuracy for detection of pancreatic NETs and metastatic disease,[29] one for detection of GEP NETs,[28] and two for pulmonary carcinoids.[30,37] In all studies, SSTR-PET/CT was associated with higher sensitivity than ^{18}FDG-PET.

For diagnosis of GEP NETs, one poor-quality study (n=27) found ^{68}Ga-DOTATATE PET/CT associated with higher sensitivity than FDG PET/CT (95% vs. 37%, per-lesion analysis;

p not reported).[28] Another poor-quality study found ^{68}Ga-DOTATOC PET/CT (n=20) associated with higher sensitivity than ^{18}FDG-PET (n=8) for detection of pancreatic NETs (100% vs. 25%, per-patient analysis; p=0.03).[29] Specificity was not reported in either study. In the latter study, SSTR-PET/CT was also associated with higher sensitivity for detection of metastatic disease (93% vs. 20%), but data were poorly reported and the difference was not statistically significant (p=0.22).

For diagnosis of pulmonary carcinoids, two studies compared accuracy of SSTR-PET/CT with ^{18}FDG PET/CT using a per-patient analysis.[30,37] One good-quality study (n=32) found ^{68}Ga-DOTATOC PET/CT associated with higher sensitivity than ^{18}FDG PET/CT (96%, 95% CI 80% to 99.9% vs. 69%, 95% CI 48% to 86%).[37] Specificity was 100% for both modalities. A poor-quality study (n=33) found ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, or ^{68}Ga-DOTANOC PET/CT associated with higher sensitivity than ^{18}FDG-PET/CT, though the difference was not statistically significant (79% vs. 55%, p=0.13).[30] In a stratified analysis from this study, SSTR-PET/CT was associated with higher sensitivity than ^{18}FDG PET/CT for typical carcinoids (91% vs. 35%, p<0.001) but worse sensitivity for atypical carcinoids (50% vs. 100%, p=0.04).

SSTR-PET Compared With CT/MRI

Ten studies (n=19 to 131) compared the diagnostic accuracy of SSTR-PET or PET/CT with CT or MRI (**Table 4c**). Two studies evaluated accuracy for detection of NETs (primarily GEP or pulmonary),[25,27] four studies evaluated accuracy for detection of GEP NETs,[26,29,31,38] four studies evaluated accuracy for detection of metastatic disease,[29,32,34,35] and one study accuracy for detection of unknown primary or metastatic NETs.[33] Across studies and tumor types, SSTR-PET was generally associated with higher sensitivity than CT or MRI, though differences were not

always statistically significant; a potential exception was similar accuracy of SSTR-PET and MRI for detection of metastatic disease.

For identification of NETs (primarily GEP or pulmonary), one good-quality study (n=84) found ^{68}Ga-DOTATOC PET associated with higher sensitivity (97% vs. 61%) and specificity (92% vs. 71%) than CT, based on a per-patient analysis (McNemar's $p<0.001$).[27] A fair-quality study (n=19) found ^{68}Ga-DOTATATE PET/CT associated with higher sensitivity (96% vs. 72%) than MRI, based on a per-lesion analysis, though the difference was not statistically significant ($p=0.08$).[25] Specificity was similar for SSTR-PET/CT and MRI (97% vs. 100%).

For identification of GEP NETs, one fair-quality study (n=19) found ^{68}Ga-DOTATOC PET/CT associated with higher sensitivity than CT for identification of duodenopancreatic NETs in MEN1 patients (76% vs. 60%, $p<0.0001$ for comparison of SSTR-PET/CT, OctreoScan, and CT), as well as higher specificity (100% vs. 50%, $p<0.01$), based on a per-lesion analysis.[31] Another fair-quality study (n=21) found ^{68}Ga-DOTATOC PET/CT associated with higher sensitivity (92% vs. 43%) and specificity (94% vs. 61%) than CT for detection of NETs in MEN1 patients (per lesion analysis, $p<0.001$).[26] A third fair-quality study found ^{68}Ga-DOTATOC PET/CT (n=19) associated with slightly higher sensitivity than CT (n=16) for detection of duodenopancreatic NETs (85% vs. 73%), but the difference was not statistically significant.[38] Specificity was similar for the two imaging modalities (83% vs. 80%). A poor-quality study (n=20) found ^{68}Ga-DOTATOC PET/CT associated with higher sensitivity than CT for detection of pancreatic NETs, based on a per-patient analysis, but the difference was not statistically significant (100% vs. 83%, $p=0.06$).[29] In this study, SSTR-PET/CT was also associated with higher sensitivity for detection of metastatic disease (93% vs. 57%), but data were poorly reported and the difference was not statistically significant ($p=0.12$).

For identification of unknown primary or metastatic NETs, one poor-quality study (n=131) found ^{68}Ga-DOTATATE PET/CT associated with higher sensitivity than CT or MRI (95% vs. 45%, per-lesion analysis; $p<0.001$).[33]

For detection of metastatic disease, one fair-quality study (n=51) found ^{68}Ga-DOTATOC PET associated with higher sensitivity than CT for detection of NET bone metastases (97% vs. 58%, $p<0.001$), based on a per-patient analysis.[32] Specificity was similar (92% vs. 99.8%). Another fair-quality study (n=51) found ^{68}Ga-DOTATOC PET/CT, MRI, and CT associated with similar sensitivity and specificity for detection of metastatic disease in persons with NETs suspected of having metastatic spread, based on a per-patient analysis.[34] Sensitivity ranged from 90% to 98% for the three modalities and specificity from 90% to 100%. Based on a per-lesion analysis, SSTR PET/CT and MRI were associated with higher sensitivity (91% to 92%) than CT (81%); specificity was higher for SSTR PET/CT (59%) than for MRI or CT (15% to 17%).

One fair-quality study (n=22) found ^{68}Ga-DOTATOC PET/CT associated with somewhat lower sensitivity than MRI for differentiating liver metastases due to NET lesions (74% vs. 88%).[35] Sensitivity of CT (68%, 95% CI 59% to 77%) was similar to SSTR-PET/CT. Specificity of all three imaging modalities was similar (85% to 88%). SSTR PET/MRI was associated with sensitivity similar to MRI (91%, 95% CI 84% to 96%) and slightly higher specificity (95%, 95% CI 88% to 99%) than the other modalities.

Key Question 1a. How does diagnostic accuracy vary according to patient or tumor characteristics (e.g., Ki-67, grade and differentiation, or site of origin)?

Evidence on how diagnostic accuracy varies according to tumor characteristics is limited. Poorly differentiated NETs tend to have poorer SSTR expression and greater glucose transport due to the rapid proliferation of cells, which may make them more amenable to detection using ^{18}FDG PET.[40] However, the only study meeting inclusion criteria that stratified diagnostic accuracy results according to tumor grade found SSTR-PET/CT associated with higher sensitivity than ^{18}FDG PET/CT for all tumor grades, though the difference in sensitivity between SSTR-PET/CT and ^{18}FDG PET/CT was most pronounced for grade 1 GEP NETs (100% vs. 17%) and less pronounced for grade 2 (91% vs. 43%) and grade 3 (92% vs. 51%).[28] One other study reported tumor grade but did not analyze results stratified according to grade.[35]

Ki-67 is an established marker of cell proliferation that is used to grade NETs,[41] but no study stratified diagnostic accuracy results according to Ki-67 index levels. Only one study[24] reported the proportion of patients within different Ki-67 categories. In this study, about 90% of patients who could be categorized were low or intermediate; however, approximately one third of patients were missing Ki-67 information.

As described above, one study found that SSTR-PET/CT was associated with higher sensitivity than ^{18}FDG PET/CT for typical pulmonary carcinoids (91% vs. 35%, $p<0.001$) but worse sensitivity for atypical carcinoids (50% vs. 100%, $p=0.04$).[30] No other study in Key Question 1 stratified diagnostic accuracy results according to NET tumor type.

Diagnostic accuracy of SSTR-PET/CT may also vary according to tumor location, due to variability across organs in physiological uptake (e.g., higher in the liver and gut). In addition, the degree of SSTR expression may vary across sites (e.g., generally lower in pancreatic than in gastrointestinal tumors). One study found that sensitivity of SSTR-PET/CT was higher than for OctreoScan or CT/MRI for detection of unknown primary or metastatic NETs across when tumors were stratified according to site (pancreas, liver, bowel, abdominal and retroperitoneal lymph nodes, bone), with the exception of lung and mediastinal NETs, for which SSTR-PET/CT and CT/MRI performed similarly (**Table 4a**).[33] For evaluation of metastatic lesions, two studies found that accuracy of SSTR-PET/CT was similar in analyses stratified according to site of metastasis (**Table 4c**).[34,36] Across the studies included in Key Question 1, there was insufficient evidence to determine whether diagnostic accuracy differed according to NET tumor site, due to small numbers of studies for each comparison, imprecise estimates, and methodological shortcomings in the studies.

Key Question 2. What is the predictive utility of SSTR-PET compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI for predicting response to PRRT or somatostatin analogue therapy?

No study compared the utility of SSTR-PET versus OctreoScan, ^{18}FDG-PET, or CT/MRI for predicting response to PRRT or somatostatin analogue therapy. However, two studies evaluated the utility of SSTR-PET, without a comparison to other imaging modalities, for predicting response to PRRT or somatostatin analogue therapy.[42,43] One study found that among patients with well-differentiated NETs of the ileum treated with octreotide, the degree of

radiotracer uptake (based on the lesion with highest uptake) as measured using SUVs (standardized uptake values) was associated with duration of progression-free survival.[42] A cutoff for the SUVmax of 29.4 and for the SUVmean of 20.3 separated between patients with a long progression-free survival (69 weeks) and short progression-free survival (26 weeks). In a multivariate Cox regression with backward stepwise model, SUV was the only significant predictor for progression-free survival (gender distribution, presence of primary tumor, and location of metastases were not predictive). However, the predictive accuracy was poor (sensitivity 75%, specificity 64%). Another study of patients with metastatic NET found an SUVmax greater than 16.4 associated with sensitivity of 95% and specificity of 60% for predicting response to PRRT.[43]

Key Question 2a. How does predictive utility vary according to patient or tumor characteristics?

No study evaluated how predictive utility varies according to patient or tumor characteristics.

Key Question 3. What are the effects of SSTR-PET imaging compared with OctreoScan, ^{18}FDG-PET, and/or CT/MRI on clinical decision-making?

Six studies addressed the effects of SSTR-PET on change in treatment management compared with imaging without SSTR-PET (**Table 4d**). Three studies were conducted in the United States,[24,33,44] two in Germany,[26,45] and one each in Belgium[36] and Austria.[27] Sample sizes

ranged from 21 to 131. Patients were enrolled with metastatic NETs,[36] MEN syndrome,[26,44] suspected or known GEP NETs,[33] proven NETs,[24,45] or a combination of suspected NETs, proven NETS, and metastatic NETs.[27] SSTR-PET or –PET/CT were compared with OctreoScan in four studies,[24,33,36,44] CT in five studies,[26,27,33,44,45] and MRI in three studies.[33,44,45]

The proportion of patients who had a change in management due to the SSTR-PET/CT ranged from as 13%[36] to 60%,[45] with most studies reporting over 30%.[24,26,33,44,45] The type of change reported in the studies included additional surgical resection, cancellation of surgery, additional indication for surgery, and additional pharmacotherapy.

All studies had methodological shortcomings (**Table 6b**). Importantly, none of the studies clearly pre-defined "change in clinical decision-making" or reported use of a formal protocol or treatment algorithm to determine responses to SSTR-PET findings. No study reported attrition, no study included a comparison group of patients who underwent SSTR-PET without the alternative imaging modality, and the studies were not designed to adjust for potential confounders. Only three of the studies reported that they enrolled consecutive patients,[24,27,45] and two studies did not blind the outcome assessor.[44,45]

Key Question 3a. How do effects on clinical decision-making vary according to patient or tumor characteristics?

There was insufficient evidence to determine how effects of SSTR-PET on decision-making vary according to patient or tumor characteristics.

DISCUSSION

The main findings of this review are summarized in **Appendix 7**. SSTR-PET was associated with greater sensitivity than OctreoScan (difference in sensitivity ranged from 14% to 56%) and ^{18}FDG-PET (difference in sensitivity ranged from 24% to 75%) for diagnosis of NETs. Findings were generally consistent for diagnosis of pulmonary NETs, GEP NETs, or both, as well as for primary and metastatic lesions. SSTR-PET was also associated with higher sensitivity for identification of primary NET than CT/MRI (differences in sensitivity ranged from 12% to 49%). For metastatic lesions, three studies reported inconsistent findings, with some studies finding no clear differences between SSTR-PET and MRI, or MRI associated with slightly higher sensitivity. Most studies reported no clear differences in specificity between SSTR-PET and alternative imaging modalities.

Evidence on how comparative diagnostic accuracy varies according to tumor characteristics is limited. One study found no clear effects of tumor grade on diagnostic accuracy differences between SSTR-PET/CT versus ^{18}FDG-PET/CT[28] and one study found SSTR-PET more accurate than ^{18}FDG-PET/CT for diagnosis of typical carcinoids, but an opposite pattern for atypical carcinoids.[30] Studies reported no clear differences in comparative diagnostic accuracy when analyses were stratified according to metastasis site or to tumor location; a possible exception was pulmonary lesions, for which one study found that SSTR-PET and CT/MRI performed similarly.[33]

No study compared the utility of SSTR-PET versus alternative imaging modalities for predicting response to PRRT or somatostatin analogue therapy. Although two studies of SSTR-PET found the degree of radiotracer uptake (as measured by SUV) associated with the likelihood

of treatment response, diagnostic accuracy was suboptimal.[42,43] In particular, specificity for predicting response to treatment was low (60% to 65%).

Although five studies found that SSTR-PET was associated with changes in management in a substantial proportion of patients, the studies had important methodological limitations. In particular, the studies did not pre-define "changes in management" or report use of standardized protocols to guide management decisions in response to SSTR-PET imaging findings, and no study included a comparison group of patients who underwent SSTR-PET without alternative imaging. No study was designed to assess clinical outcomes associated with use of SSTR-PET.

Limitations of this review include the relatively small number of studies available for specific imaging comparisons and types of NETs, the lack of evidence on how patient and tumor characteristics impact diagnostic accuracy, and methodological limitations in the studies, including suboptimal and heterogeneous reference standards and use of a case-control design in a number of studies. Most studies appeared to evaluate accuracy for diagnosis of more well-differentiated/indolent NETs, though details about tumor grade and type were relatively limited. Most studies reported results based on per-lesion analyses, which may not be as clinically relevant as per-patient analyses. Per-lesion analyses may also result in higher precision of estimates than warranted, since one patient may have many lesions. Some studies were not designed to or failed to report specificity, providing incomplete information regarding diagnostic accuracy. Due to the heterogeneity among studies, we did not attempt meta-analysis. We focused on standard radiotracers for SSTR-PET (^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC) and octreotide SPECT/CT (^{111}In-DTPA), although other radiotracers have been investigated.

Research that focuses on comparative diagnostic accuracy in persons with high-grade or poorly differentiated NETs would be helpful for better understanding the usefulness and potential limitations of SSTR-PET for diagnosis. One study found that SSTR-PET/MRI performed better than SSTR-PET/CT for detection of metastatic disease;[35] more research would be useful for understanding the comparative performance of these two modalities. Research is also needed to understand the predictive utility of SSTR-PET for guiding decisions regarding use of PRRT and somatostatin analogue therapy. Future studies on effects of SSTR-PET should utilize pre-defined protocols or algorithms to guide clinical decisions, clearly define "treatment changes," and compare decision-making among groups who undergo alternative imaging protocols.

REFERENCES

1. Zacharof AK. Gastrointestinal neuroendocrine tumors. Ann Gastroenterol. 2003; 16(1):34-9.
2. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010; 39(6):707-12. doi: 10.1097/MPA.0b013e3181ec124e. PMID: 20664470.
3. Kunz PL. Carcinoid and neuroendocrine tumors: building on success. J Clin Oncol. 2015; 33(16):1855-63. doi: 10.1200/jco.2014.60.2532. PMID: 25918282.
4. Bison SM, Konijnenberg MW, Melis M, et al. Peptide receptor radionuclide therapy using radiolabeled somatostatin analogs: focus on future developments. Clin Transl Imaging. 2014; 2(1):55-66. doi: 10.1007/s40336-014-0054-2. PMID: PMC3991004.
5. de Herder WW, Kwekkeboom DJ, Feelders RA, et al. Somatostatin receptor imaging for neuroendocrine tumors. Pituitary. 2006; 9(3):243-8. doi: 10.1007/s11102-006-0270-5. PMID: 17001462.
6. Heller MT, Shah AB. Imaging of neuroendocrine tumors. Radiol Clin North Am. 2011; 49(3):529-48. doi: http://dx.doi.org/10.1016/j.rcl.2011.02.011.
7. Kwekkeboom DJ, Krenning EP. Somatostatin receptor imaging. Semin Nucl Med. 2002; 32(2):84-91. doi: 10.1053/snuc.2002.31022. PMID: 11965603.
8. Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. Semin Nucl Med. 2006; 36(3):228-47. PMID: 16762613.
9. Shi W, Johnston CF, Buchanan KD, et al. Localization of neuroendocrine tumours with [111In] DTPA-octreotide scintigraphy (Octreoscan): a comparative study with CT and MR imaging. QJM. 1998; 91(4):295-301. PMID: 9666953.
10. Krausz Y, Keidar Z, Kogan I, et al. SPECT/CT hybrid imaging with 111In-pentetreotide in assessment of neuroendocrine tumours. Clin Endocrinol (Oxf). 2003; 59(5):565-73. PMID: 14616879.
11. Breeman WAP, de Blois E, Sze Chan H, et al. 68Ga-labeled DOTA-peptides and 68Ga-labeled radiopharmaceuticals for positron emission tomography: current status of research, clinical applications, and future perspectives. Semin Nucl Med. 2011; 41(4):314-21. doi: http://dx.doi.org/10.1053/j.semnuclmed.2011.02.001. PMID: 21624565
12. Mojtahedi A, Thamake S, Tworowska I, et al. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. Am J Nucl Med Mol Imaging. 2014; 4(5):426-34. PMID: PMC4138137.
13. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2013; 40(11):1770-80. doi: http://dx.doi.org/10.1007/s00259-013-2482-z. PMID: 23873003.
14. Yang J, Kan Y, Ge BH, et al. Diagnostic role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. Acta Radiol. 2014; 55(4):389-98. doi: http://dx.doi.org/10.1177/0284185113496679. PMID: 23928010.
15. Shea BJ, Bouter LM, Peterson J, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007; 2(12):e1350. doi: 10.1371/journal.pone.0001350. PMID: 18159233.
16. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007; 7:10. doi: 10.1186/1471-2288-7-10. PMID: 17302989.
17. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009; 62(10):1013-20. doi: 10.1016/j.jclinepi.2008.10.009. PMID: 19230606.
18. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure

Manual. 2015. https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes Accessed April 11, 2017.
19. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009. PMID: 22007046.
20. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004; 328(7454):1490. doi: 10.1136/bmj.328.7454.1490. PMID: 15205295.
21. Agency for Healthcare Research Quality. Methods guide for effectiveness and comparative effectiveness reviews. 2014; AHRQ Publication No. 10(14)-EHC063-EF.
22. Singh S, Chang SM, Matchar DB, et al. Chapter 7: grading a body of evidence on diagnostic tests. J Gen Intern Med. 2012; 27 Suppl 1:S47-55. doi: 10.1007/s11606-012-2021-9. PMID: 22648675.
23. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008; 336(7653):1106-10. doi: 10.1136/bmj.39500.677199.AE. PMID: 18483053.
24. Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of 68Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. J Nucl Med. 2016; 57(5):708-14. doi: 10.2967/jnumed.115.163865. PMID: 26769865.
25. Etchebehere EC, de Oliveira Santos A, Gumz B, et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. J Nucl Med. 2014; 55(10):1598-604. doi: 10.2967/jnumed.114.144543. PMID: 25168627.
26. Froeling V, Elgeti F, Maurer MH, et al. Impact of Ga-68 DOTATOC PET/CT on the diagnosis and treatment of patients with multiple endocrine neoplasia. Ann Nucl Med. 2012; 26(9):738-43. doi: 10.1007/s12149-012-0634-z. PMID: 22865406
27. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med. 2007; 48(4):508-18. PMID: 17401086.
28. Has Simsek D, Kuyumcu S, Turkmen C, et al. Can complementary 68Ga-DOTATATE and 18F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? J Nucl Med. 2014; 55(11):1811-7. doi: 10.2967/jnumed.114.142224. PMID: 25315243.
29. Kumar R, Sharma P, Garg P, et al. Role of 68Ga-DOTATOC PET-CT in the diagnosis and staging of pancreatic neuroendocrine tumours. Eur Radiol. 2011; 21(11):2408. doi: 10.1007/s00330-011-2199-y. PMID: 21750886.
30. Lococo F, Perotti G, Cardillo G, et al. Multicenter comparison of 18F-FDG and 68Ga-DOTA-peptide PET/CT for pulmonary carcinoid. Clin Nucl Med. 2015; 40(3):e183-9. doi: 10.1097/rlu.0000000000000641. PMID: 25608152.
31. Morgat C, Velayoudom-Cephise FL, Schwartz P, et al. Evaluation of 68 Ga-DOTA-TOC PET/CT for the detection of duodenopancreatic neuroendocrine tumors in patients with MEN1. Eur J Nucl Med Mol Imaging. 2016; 43(7):1258-66. PMID: 26819103.
32. Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. J Nucl Med. 2009; 50(8):1214-21. doi: 10.2967/jnumed.108.060236. PMID: 19617343.
33. Sadowski SM, Neychev V, Millo C, et al. Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. J Clin Oncol. 2016; 34(6):588-96. doi: http://dx.doi.org/10.1200/JCO.2015.64.0987 . PMID: 26712231.
34. Schraml C, Schwenzer NF, Sperling O, et al. Staging of neuroendocrine tumours: comparison of [(68)Ga]DOTATOC multiphase PET/CT and whole-body MRI. Cancer Imaging. 2013; 13(1):63-72. doi: 10.1102/1470-7330.2013.0007. PMID: PMC3589947.

35. Schreiter NF, Nogami M, Steffen I, et al. Evaluation of the potential of PET-MRI fusion for detection of liver metastases in patients with neuroendocrine tumours. Eur Radiol. 2012; 22(2):458-67. doi: 10.1007/s00330-011-2266-4. PMID: 21904802.
36. Van Binnebeek S, Vanbilloen B, Baete K, et al. Comparison of diagnostic accuracy of (111)In-pentetreotide SPECT and (68)Ga-DOTATOC PET/CT: A lesion-by-lesion analysis in patients with metastatic neuroendocrine tumours. Eur Radiol. 2016; 26(3):900-9. doi: http://dx.doi.org/10.1007/s00330-015-3882-1. PMID: 26162577.
37. Venkitaraman B, Karunanithi S, Kumar A, et al. Role of 68Ga-DOTATOC PET/CT in initial evaluation of patients with suspected bronchopulmonary carcinoid. Eur J Nucl Med Mol Imaging. 2014; 41(5):856-64. doi: 10.1007/s00259-013-2659-5. PMID: 24435773.
38. Versari A, Camellini L, Carlinfante G, et al. Ga-68 DOTATOC PET, endoscopic ultrasonography, and multidetector CT in the diagnosis of duodenopancreatic neuroendocrine tumors: a single-centre retrospective study. Clin Nucl Med. 2010; 35(5):321-8. doi: 10.1097/RLU.0b013e3181d6677c. PMID: 20395703.
39. Arora S, Geppert CM, Kalishman S, et al. Academic health center management of chronic diseases through knowledge networks: Project ECHO. Acad Med. 2007; 82(2):154-60. doi: 10.1097/ACM.0b013e31802d8f68. PMID: 17264693.
40. Garcia-Carbonero R, Garcia-Figueiras R, Carmona-Bayonas A, et al. Imaging approaches to assess the therapeutic response of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): current perspectives and future trends of an exciting field in development. Cancer Metastasis Rev. 2015; 34(4):823-42. doi: 10.1007/s10555-015-9598-5. PMID: 26433592.
41. Nadler A, Cukier M, Rowsell C, et al. Ki-67 is a reliable pathological grading marker for neuroendocrine tumors. Virchows Arch. 2013; 462(5):501-5. doi: 10.1007/s00428-013-1410-8. PMID: 23588555.
42. Koch W, Auernhammer CJ, Geisler J, et al. Treatment with octreotide in patients with well-differentiated neuroendocrine tumors of the ileum: prognostic stratification with Ga-68-DOTA-TATE positron emission tomography. Mol Imaging. 2014; 13:1-10. PMID: 24824963.
43. Kratochwil C, Stefanova M, Mavriopoulou E, et al. SUV of [68Ga]DOTATOC-PET/CT predicts response probability of PRRT in neuroendocrine tumors. Mol Imaging Biol. 2014; 17(3):313-8. doi: http://dx.doi.org/10.1007/s11307-014-0795-3. PMID: 25319765.
44. Sadowski SM, Millo C, Cottle-Delisle C, et al. Results of (68)Gallium-DOTATATE PET/CT scanning in patients with multiple endocrine neoplasia type 1. J Am Coll Surg. 2015; 221(2):509-17. doi: http://dx.doi.org/10.1016/j.jamcollsurg.2015.04.005. PMID: 26206648.
45. Frilling A, Sotiropoulos GC, Radtke A, et al. The impact of 68Ga-DOTATOC positron emission tomography/computed tomography on the multimodal management of patients with neuroendocrine tumors. Ann Surg. 2010; 252(5):850-6. doi: 10.1097/SLA.0b013e3181fd37e8. PMID: 21037441.

Appendix 1. Table of Systematic Reviews

Author, Year	Purpose of Study	Databases Searched Date of Last Search	Number of Included Studies	Types of Studies Included/ Limitations of Primary Studies	Language Restrictions
Geijer, 2013	To evaluate the diagnostic quality of SMSR PET and perform a meta-analysis as an update of a previous study (Treglia, 2012).	Pubmed/MEDLINE and Embase through December 2012	22	Diagnostic accuracy studies; studies were often in highly selected populations and many in patients with known tumors, so false-positive results could not be determined.	None
Yang, 2014	To systematically review and perform a meta-analysis of published data regarding the diagnostic role of 68Ga-DATATOC and 68Ga-DOTATATE PET in the diagnosis of NETs.	Pubmed, Embase, and Scopus through April 2013	10	Diagnostic accuracy studies; studies were rated as moderate-high quality, but specific details about limitations were NR.	None

Appendix 1. Table of Systematic Reviews

Author, Year	Methods for Rating Methodological Quality of Primary Studies	Methods for Synthesizing Results of Primary Studies	Number of Patients	Tracer and Imagining Scan Evaluated	Reference Standard
Geijer, 2013	QUADAS-2	Pooled all studies, conducted meta-analysis, and reported sensitivity and specificity with 95% CIs	2,105 total	68Ga-DOTATOC PET or PET/CT (11 studies) 68Ga-DOTATATE PET/CT (7 studies) 68Ga-Da-DOTANOC PET/CT (3 studies) 68Cu-DOTATE PET/CT (1 study)	Histology with or without clinical/imaging follow-up, biopsy, laboratory analysis, or CT
Yang, 2014	QUADAS	Pooled studies separately by tracer (68Ga-DOTATOC or 68Ga-DOTATATE), conducted meta-analyses, and reported sensitivity and specificity with 95% CIs	416 total	68Ga-DOTATOC PET or PET/CT (6 studies) 68Ga-DOTATATE PET/CT (4 studies)	Histology with or without follow-up

Appendix 1. Table of Systematic Reviews

Author, Year	Results	Adverse Events
Geijer, 2013	Pooled sensitivity (95% CI): 93% (91 to 94); range: 70% to 100%, I-square: 72% Pooled specificity: 96% (95 to 98); range: 67% to 100% Area under SROC 0.98 (0.95 to 1.0), I-square: 68%	Not reported
Yang, 2014	**68Ga-DOTATOC vs. 68Ga-DOTATATE** Pooled sensitivity (95% CI): 93% (89 to 96) vs. 96% (91 to 99), I-square: 80.9% vs. 60.5% Pooled specificity (95% CI): 85% (74 to 93) vs. 100% (82 to 100), I-square: 56.8% vs. 0% AUROC: 0.96 vs. 0.98	Not reported

Abbreviations: CI=confidence interval; NET= neuroendocrine tumor; QUADAS=quality assessment of diagnostic accuracy studies; PET= positron emission tomography.

Appendix 2. Search Strategies

Database: Ovid MEDLINE(R) without Revisions <1996 to November Week 2 2016>
Search Strategy:
---
1 exp Somatostatin/ (7384)
2 Receptors, Somatostatin/ (3380)
3 (somatostatin receptors or SSTR).mp. (1904)
4 Positron-Emission Tomography/ (41516)
5 PET.ti,ab. (54583)
6 exp Tomography, X-Ray Computed/ (261479)
7 (DOTATOC or DOTATATE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (602)
8 exp Neuroendocrine Tumors/ (82976)
9 neuroendocrine.mp. (29160)
10 or/1-3 (9788)
11 or/4-7 (310902)
12 8 or 9 (101994)
13 and/10-12 (482)

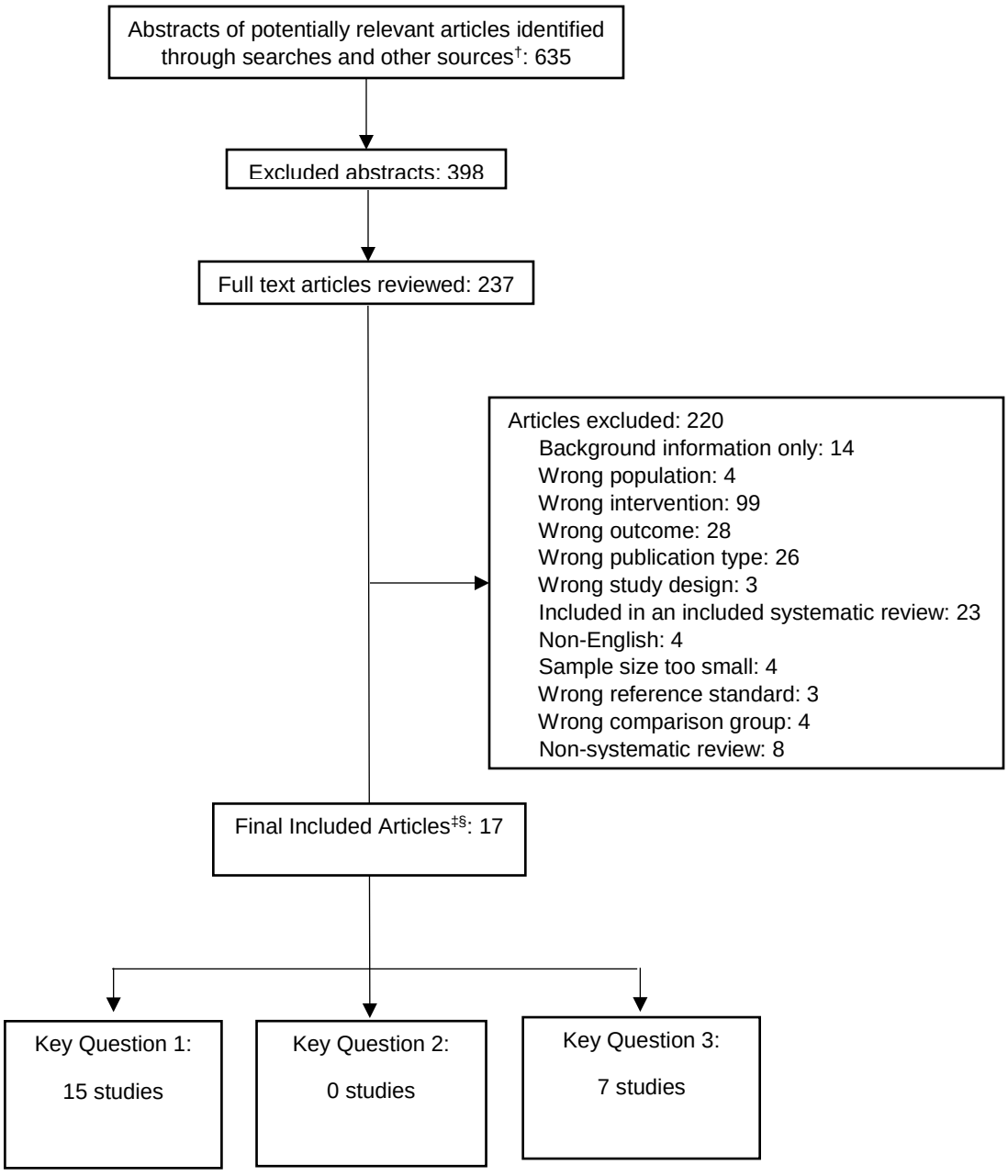
Database: Ovid MEDLINE(R) without Revisions <1996 to November Week 2 2016>
Search Strategy:
---
1 exp Somatostatin/ (7384)
2 Receptors, Somatostatin/ (3380)
3 (somatostatin receptors or SSTR).mp. (1904)
4 Positron-Emission Tomography/ (41516)
5 PET.ti,ab. (54583)
6 exp Tomography, X-Ray Computed/ (261479)
7 (DOTATOC or DOTATATE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (602)
8 exp Neuroendocrine Tumors/ (82976)
9 neuroendocrine.mp. (29160)
10 or/1-3 (9788)
11 or/4-7 (310902)
12 8 or 9 (101994)
13 and/10-12 (482)
14 octreoscan.mp. (308)
15 fdg-pet.mp. (14936)
16 CT MRI.mp. (2581)
17 14 or 15 or 16 (17578)
18 12 and 17 (1031)
19 18 not 13 (934)

Appendix 2. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2016>
Search Strategy:
---
1 exp Somatostatin/ (536)
2 Receptors, Somatostatin/ (32)
3 (somatostatin receptors or SSTR).mp. (59)
4 Positron-Emission Tomography/ (789)
5 PET.ti,ab. (2435)
6 exp Tomography, X-Ray Computed/ (3949)
7 (DOTATOC or DOTATATE).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (28)
8 exp Neuroendocrine Tumors/ (1267)
9 neuroendocrine.mp. (1405)
10 or/1-3 (600)
11 or/4-7 (6408)
12 8 or 9 (2598)
13 and/10-12 (11)
14 octreoscan.mp. (8)
15 fdg-pet.mp. (729)
16 CT MRI.mp. (292)
17 14 or 15 or 16 (1004)
18 12 and 17 (25)
19 13 or 18 (33)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 16, 2016>
Search Strategy:
---
1 somatostatin.mp. [mp=title, short title, abstract, full text, keywords, caption text] (45)
2 SSTR.mp. [mp=title, short title, abstract, full text, keywords, caption text] (1)
3 PET.ti,ab. (19)
4 (DOTATOC or DOTATATE).mp. [mp=title, short title, abstract, full text, keywords, caption text] (1)
5 octreoscan.mp. [mp=title, short title, abstract, full text, keywords, caption text] (2)
6 fdg pet.mp. [mp=title, short title, abstract, full text, keywords, caption text] (30)
7 ct mri.mp. [mp=title, short title, abstract, full text, keywords, caption text] (95)
8 or/1-7 (165)
9 8 and neuroendocrine.mp. [mp=title, short title, abstract, full text, keywords, caption text] (8)

Appendix 3. Literature Flow Diagram



†Identified from reference lists, hand searching, suggested by experts, etc.
‡Studies that provided data and contributed to the body of evidence were considered 'included'
§Studies may contribute data to more than one key question

Appendix 4. Evidence Tables

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Deppen, 2016[24] Fair	^{68}Ga-DOTATATE	PET/CT	Unclear	Single or multiple CT or MRI scans, surgical tissue confirmation, or combination thereof.	Prospective cross-sectional	USA
Deppen, 2016[24] Fair	^{111}In-Pentetreotide	SPECT or SPECT/CT	Unclear	Same as above	Same as above	Same as above
Deppen, 2016[24] Fair	^{68}Ga-DOTATATE	PET/CT	Unclear	Same as above	Same as above	Same as above
Deppen, 2016[24] Fair	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Deppen, 2016[24] Fair	Enrolled patients having a proven diagnosis of NET, prospective analysis of safety and toxicity data and ^{68}Ga-DOTATATE scan findings. Patients were excluded if no prior ^{111}In-Pentetreotide was available, time between scans exceeded 3 years, no 111In-Pentetreotide scan available after a major surgical intervention occuring between the scans.	Age (mean, years): 53.7 (SD 11) Female: 58% NET type: -Midgut carcinoid: 45% -Gastroenteropancreatic: 23% -Unknown primary: 12% -Symptoms only: 7% -Pulmonary: 7% -Hindgut or rectal: 3% -Other: 2% Ki-67 category: -Low: 24 -Intermediate: 37 -High: 6 -Missing: 30	N=97 100%	Detection of cancer or progression, all types, per-patient analysis	48	2	2	26	96% (86 to 100)
Deppen, 2016[24] Fair	Same as above	Same as above	Same as above	Detection of cancer or progression, all types, per-patient analysis	36	2	14	26	72% (58 to 75)
Deppen, 2016[24] Fair	Same as above	NR for subgroup	N=50 100%	Detection of cancer or progression, all types, per-patient analysis, only those who underwent SPECT/CT	28	1	1	18	97% (82 to 100)
Deppen, 2016[24] Fair	Same as above	Same as above	Same as above	Detection of cancer or progression, all types, per-patient analysis, only those who underwent SPECT/CT	24	1	5	18	83% (64 to 94)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Deppen, 2016[24] Fair	96% (86.29 to 99.51)	93% (77 to 99)	92.86% (76.50 to 99.12)	96% (86 to 100)	96% (86.31 to 98.92)	93% (77 to 99)	92.86% (76.91 to 98.07)
Deppen, 2016[24] Fair	72% (57.51 to 83.77)	93% (77 to 99)	92.86% (76.50 to 99.12)	95% (82 to 99)	94.74% (82.40 to 98.58)	65% (48 to 94)	65% (54.06 to 74.56)
Deppen, 2016[24] Fair	96.55% (82.24 to 99.91)	93% (77 to 99)	94.74% (73.97 to 99.87)	NR	96.55% (80.58 to 99.47)	NR	94.74% (72.34 to 99.20)
Deppen, 2016[24] Fair	82.76% (64.23 to 94.15)	93% (77 to 99)	94.74% (73.97 to 99.87)	NR	96% (77.96 to 99.39)	NR	78.26% (61.69 to 88.95)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Deppen, 2016[24] Fair	NR	13.44 (3.53 to 51.16)	NR	0.04 (0.01 to 0.17)	NR	NR	0.94 (0.89 to 1.00)
Deppen, 2016[24] Fair	NR	10.08 (2.62 to 38.75)	NR	0.30 (0.19 to 0.48)	NR	NR	0.82 (0.74 to 0.90)
Deppen, 2016[24] Fair	NR	18.34 (2.72 to 123.76)	NR	0.04 (0.01 to 0.25)	NR	NR	NR
Deppen, 2016[24] Fair	NR	15.72 (2.32 to 106.71)	NR	0.18 (0.08 to 0.41)	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Etchebehere, 2014[25] Fair	^{68}Ga-DOTATATE	PET/CT	Intense focal uptake in comparision to the adjacent tissues was seen in the coronal, transaxial, and sagittal views.	Consensus among investigators at the end of the study evaluating all lesions by all methods, clinical follow-up, and biopsy of suggestive lesions when possible.	Prospective cross-sectional	Brazil Setting: NR
Etchebehere, 2014[25] Fair	111-185 MBq (3-5 mCi) of ^{99m}Tc-HYNIC-octreotide	SPECT/CT	Intense focal uptake in comparision to the adjacent tissues was seen in the coronal, transaxial, and sagittal views.	Same as above	Same as above	Same as above
Etchebehere, 2014[25] Fair	Not applicable	MRI	Analzyed in terms of number, size, location, and signal intensity and were compared with the T1-weighted and short-τ inversion recovery sequences to rule out false-positive findings. Lymph nodes were defined as malignant according to the diameter of the small axis.	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Etchebehere, 2014[25] Fair	Patients ≥18 years old with a histologic diagnosis of NET, suspected tumor recurrence, no prior history of toher malignant primary neoplasms, nonlactating and nonpregnant, undergo all imagining studies within an interval of ≤3 months, and receive no treatment or intervention during the imagining period.	Age (mean, years): 54.3; range: 34-77 Female: 47% Primary site -Bronchi: 22% -Pancreas: 31% -Gut: 31% -Unknown: 16% Ki-67 (mean): 9.5%; range: 1-26% Chromogranin A (mean, ng/mL): 151.5; range: 1.6 to 901 Clinical follow-up (mean, months): 4	N=19 100%	Detection of NETs, per-lesion analysis	NR	NR	NR	NR	96%
Etchebehere, 2014[25] Fair	Same as above	Same as above	Same as above	Detection of NETs, per-lesion analysis	NR	NR	NR	NR	60%
Etchebehere, 2014[25] Fair	Same as above	Same as above	Same as above	Detection of NETs, per-lesion analysis	NR	NR	NR	NR	72%

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Etchebehere, 2014[25] Fair	Unable to calculate	97%	Unable to calculate	94%	Unable to calculate	98%	Unable to calculate
Etchebehere, 2014[25] Fair	Unable to calculate	99%	Unable to calculate	96%	Unable to calculate	83%	Unable to calculate
Etchebehere, 2014[25] Fair	Unable to calculate	100%	Unable to calculate	100%	Unable to calculate	88%	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Etchebehere, 2014[25] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	97%
Etchebehere, 2014[25] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	86%
Etchebehere, 2014[25] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	91%

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Froeling, 2012[26] Fair	^{68}Ga-DOTATOC	PET	Blinded radiologists and nuclear medicine physicians analyzed PET and CT separately first, then PET/CT. Lesions were characterized on a 3-point scale: non-MEN-associated lesions, equivocal lesions, MEN-associated lesions.	Histopathologic proof or confirmed by clinical and radiologic follow-up.	Retrospective	Germany Setting unclear
Froeling, 2012[26] Fair	^{68}Ga-DOTATOC	PET/CT	Same as above	Same as above	Same as above	Same as above
Froeling, 2012[26] Fair	Not applicable	CT	Same as above	Same as above	Same as above	Same as above
Gabriel, 2007[27] Good	^{68}Ga-DOTATOC	PET	Clearly demarked findings with higher tracer uptake compared with liver uptake, tracer accumulation in structures that did not take up tracer physiologically or was higher than background activity, or pancreatic head: irregular or protrusive shape of finding; clear delineation fro madjacent tissue with higher uptake than liver uptake.	Histological confirmation and repeated clinical examinations with CT or MRI after 3 or 6 months for positive findings and follow-up imaging after 6 months for negative scans.	Prospective cohort	Austria Department of Nuclear Medicine
Gabriel, 2007[27] Good	Not applicable	CT	Specific appearance of malignant disease derived from NET.	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Significant accumulation of the tracer based on cisual assessment	Histology.	Prospective cross-sectional	Turkey Setting: NR
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Froeling, 2012[26] Fair	MEN syndrome verified histopathologically or by clinical parameters and imagin modalities.	Age (mean, years): 41.4; range: 16-78 Female: 48%	N=21 100%	Detection of NET lesions	NR	NR	NR	NR	85%
Froeling, 2012[26] Fair	Same as above	Same as above	Same as above	Detection of NET lesions	NR	NR	NR	NR	92%
Froeling, 2012[26] Fair	Same as above	Same as above	Same as above	Detection of NET lesions	NR	NR	NR	NR	43%
Gabriel, 2007[27] Good	Unclear	Age (mean, years): 58.2; range: 28-79 Female: 43% Enrolled for initial detection: 15% Enrolled for staging: 43% Enrolled for posttherapy follow-up: 42%	N=84 84%	Detection of NETs, per-patient analysis	69	1	2	12	97%
Gabriel, 2007[27] Good	Same as above	Same as above	Same as above	Detection of NETs, per-patient analysis	41	5	26	12	61%
Has Simsek, 2014[28] Poor	Patients with histologically proven GEP NETs	Age (mean, years): 56; range: 33-79 Female: 63%	N=27 100%	Detection of GEP NETs overall, per-lesion analysis	NR	5	NR	NR	95%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs overall, per-lesion analysis	NR	8	NR	NR	37%

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Froeling, 2012[26] Fair	Unable to calculate	97%	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Froeling, 2012[26] Fair	Unable to calculate	94%	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Froeling, 2012[26] Fair	Unable to calculate	61%	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Gabriel, 2007[27] Good	97.18% (90.19 to 99.66)	92%	92.31% (63.97 to 99.81)	NR	98.57% (91.30 to 99.78)	NR	85.71% (60.26 to 95.96)
Gabriel, 2007[27] Good	61.19% (48.50 to 72.86)	71%	70.59% (44.04 to 89.69)	NR	89.13% (79.30 to 94.61)	NR	31.58% (23.10 to 41.49)
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	94%	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	36%	Unable to calculate	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Froeling, 2012[26] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Froeling, 2012[26] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Froeling, 2012[26] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Gabriel, 2007[27] Good	NR	12.63 (1.92 to 83.09)	NR	0.03 (0.01 to 0.12)	NR	NR	96%
Gabriel, 2007[27] Good	NR	2.08 (0.97 to 4.45)	NR	0.55 (0.36 to 0.84)	NR	NR	63%
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Same as above	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the liver, per-lesion analysis	NR	NR	NR	NR	95%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the liver, per-lesion analysis	NR	NR	NR	NR	40%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bone, per-lesion analysis	NR	NR	NR	NR	95%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bone, per-lesion analysis	NR	NR	NR	NR	28%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the lymph nodes, per-lesion analysis	NR	NR	NR	NR	90%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the lymph nodes, per-lesion analysis	NR	NR	NR	NR	28%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs primary lesions, per-lesion analysis	NR	NR	NR	NR	93%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs primary lesions, per-lesion analysis	NR	NR	NR	NR	75%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs Grade 1, per-lesion analysis	NR	NR	NR	NR	100%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs Grade 1, per-lesion analysis	NR	NR	NR	NR	17%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs Grade 2, per-lesion analysis	NR	NR	NR	NR	91%

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{68}Ga-DOTATATE	PET/CT	Same as above	Same as above	Same as above	Same as above
Has Simsek, 2014[28] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Kumar, 2011[29] Poor	^{68}Ga-DOTATOC	PET/CT	Any non physiological uptake more than surrounding tissue.	Biopsy/histopathology	Prospective cohort	India Setting: NR
Kumar, 2011[29] Poor	^{18}F-FDG	PET/CT	Any non physiological focal area of increased ^{18}F-FDG uptake was looked for, keeping physiological tracer distribution in perspective.	Same as above	Same as above	Same as above
Kumar, 2011[29] Poor	Not applicable	Contrast enhanced CT	Assessed by experienecd radiologists for evidnce of primary/metastatic disease.	Same as above	Same as above	Same as above
Kumar, 2011[29] Poor	^{68}Ga-DOTATOC	PET/CT	Any non physiological uptake more than surrounding tissue.	Clinical follow-up, MRI, and/or biopsy.	Same as above	Same as above
Kumar, 2011[29] Poor	^{18}F-FDG	PET/CT	Any non physiological focal area of increased ^{18}F-FDG uptake was looked for, keeping physiological tracer distribution in perspective.	Clinical follow-up, MRI, and/or biopsy.	Same as above	Same as above
Kumar, 2011[29] Poor	Not applicable	CE-CT	Assessed by experienecd radiologists for evidnce of primary/metastatic disease.	Clinical follow-up, MRI, and/or biopsy.	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs Grade 2, per-lesion analysis	NR	NR	NR	NR	43%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs Grade 3, per-lesion analysis	NR	NR	NR	NR	92%
Has Simsek, 2014[28] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs Grade 3, per-lesion analysis	NR	NR	NR	NR	51%
Kumar, 2011[29] Poor	Patients with clinically suspected and/or histopathologically proven pancreatic NET who underwent ^{68}Ga-DOTATOC PET/CT imaging for staging and/or localisation of primary lesion.	Age (median, years): 42.5; IQR: 37.5-54.5 Female: 50% Serum chromogranin (median, ng/ml): 316; IQR: 251.5-745.5	N=20 100%	Detection of primary NETs, per-patient analysis	20	0	0	0	100% (83.01 to 100)
Kumar, 2011[29] Poor	Same as above	Same as above	N=8 100%	Detection of primary NETs, per-patient analysis	2	0	6	0	25% (3.9 to 64.9)
Kumar, 2011[29] Poor	Same as above	Same as above	N=20 100%	Detection of primary NETs, per-patient analysis	16	2	3	0	83.3% (58.5 to 96.2)
Kumar, 2011[29] Poor	Same as above	Same as above	N=20 100%	Detection of metastatic disease	13	1	Unclear	Unclear	92.8% (66 to 98.8)
Kumar, 2011[29] Poor	Same as above	Same as above	N=8 100%	Detection of metastatic disease	2	Unclear	Unclear	Unclear	20% (3.1 to 55.5)
Kumar, 2011[29] Poor	Same as above	Same as above	N=20 100%	Detection of metastatic disease	7	Unclear	Unclear	Unclear	57.1% (28.9 to 82.2)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Has Simsek, 2014[28] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Kumar, 2011[29] Poor	100% (83.16 to 100)	NR	Unable to calculate	100% (83.01 to 100)	100% (83.16 to 100)	NR	Unable to calculate
Kumar, 2011[29] Poor	25% (3.19 to 65.09)	NR	Unable to calculate	100% (19.2 to 100)	100% (63.06 to 100)	NR	Unable to calculate
Kumar, 2011[29] Poor	84.21% (60.42 to 96.62)	NR	0% (0 to 84.19)	88.2% (63.5 to 98.2)	88.89% (86.82 to 90.67)	NR	Unable to calculate
Kumar, 2011[29] Poor	Unable to calculate	100% (54 to 100)	Unable to calculate	100% (75.1 to 100)	Unable to calculate	85.7% (42.2 to 97.6)	Unable to calculate
Kumar, 2011[29] Poor	Unable to calculate	100% (16.5 to 100)	Unable to calculate	100% (19.2 to 100)	Unable to calculate	11.1% (1.8 to 48.2)	Unable to calculate
Kumar, 2011[29] Poor	Unable to calculate	100% (54 to 100)	Unable to calculate	100% (62.9 to 100)	Unable to calculate	50% (21.2 to 78.7)	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Has Simsek, 2014[28] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Kumar, 2011[29] Poor	NR	1	NR	Unable to calculate	NR	NR	NR
Kumar, 2011[29] Poor	NR	0.25	NR	Unable to calculate	NR	NR	NR
Kumar, 2011[29] Poor	NR	0.84 (0.69 to 1.02)	NR	Unable to calculate	NR	NR	NR
Kumar, 2011[29] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Kumar, 2011[29] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Kumar, 2011[29] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Lococo, 2015[30] Poor	^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE or ^{68}Ga-DOTANOC	PET/CT	Any focal accumulation of each tracer in the lung nodule higher than the surrounding uptake.	Histological diagnosis.	Retrospective	Italy 2 PET/CT centers
Lococo, 2015[30] Poor	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Morgat, 2016[31] Fair	^{68}Ga-DOTATOC	PET/CT	Focally increased uptake, compared with that of the surrounding tissue.	Combination of unblinded analysis of the CE-CT with complementary investigations (MRI, EUS, ^{18}F-FDG PET, or histology, performed on an individual basis) results.	Retrospective	France University hospital
Morgat, 2016[31] Fair	^{111}In-Pentetreotide	SPECT/CT	Increased uptake was assessed by comparison with uptake by liver tissue, according to the European Assocation of Nuclear Medicine recommendations.	Combination of unblinded analysis of the CE-CT with complementary investigations (MRI, EUS, ^{18}F-FDG PET, or histology, performed on an individual basis) results.	Same as above	Same as above
Morgat, 2016[31] Fair	2 ml/kg iohexol contrast media	CE-CT	Radiologist's blinded reading	Combination of unblinded analysis of the CE-CT with complementary investigations (MRI, EUS, ^{18}F-FDG PET, or histology, performed on an individual basis) results.	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Lococo, 2015[30] Poor	Availability of clinical charts; chest CT, ^{18}F-FDG PET/CT, and ^{68}Ga-DOTA-peptide PET/CT performed in a 2-month period; and the availability of a postsurgical histopathological diagnosis.	Age (mean, years): 59.7 (SD 14.0) Female: 64% Stage I: 49% Stage II: 36% Stage III/IV: 15%	N=33 100%	Detection of pulmonary carcinoids, per-patient analysis	26	-	7	-	79% (63 to 90)
Lococo, 2015[30] Poor	Same as above	Same as above	Same as above	Detection of pulmonary carcinoids, per-patient analysis	18	-	15	-	55% (38 to 71)
Morgat, 2016[31] Fair	Genetically confirmed MEN1 patients previously evaluated and treated at authors' department	Age (mean, years): 47; range: 26-70 Female: 63% Hyperparathyroidism: 100%	N=19 100%	Detection of duodenopancreatic NETs, per-lesion analysis	57	0	18	4	76%
Morgat, 2016[31] Fair	Same as above	Same as above	Same as above	Detection of duodenopancreatic NETs, per-lesion analysis	15	2	60	2	20%
Morgat, 2016[31] Fair	Same as above	Same as above	Same as above	Detection of duodenopancreatic NETs, per-lesion analysis	45	2	30	2	60%

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Lococo, 2015[30] Poor	78.79% (61.09 to 91.02)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate
Lococo, 2015[30] Poor	54.55% (36.35 to 71.89)	NR	Unable to calculate	NR	100% (89.42 to 100)	NR	Unable to calculate
Morgat, 2016[31] Fair	76% (64.75 to 85.11)	100%	100% (39.76 to 100)	NR	100.00%	NR	18.18% (12.93 to 24.95)
Morgat, 2016[31] Fair	20% (11.65 to 30.83)	50%	50% (6.76 to 93.24)	NR	88.24% (71.82 to 95.67)	NR	3.23% (1.23 to 8.21)
Morgat, 2016[31] Fair	60% (48.04 to 71.15)	50%	50% (6.76 to 93.24)	NR	95.74% (89.25 to 98.39)	NR	6.25% (2.35 to 15.58)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Lococo, 2015[30] Poor	NR	0.79	NR	Unable to calculate	NR	NR	NR
Lococo, 2015[30] Poor	NR	0.55	NR	Unable to calculate	NR	NR	NR
Morgat, 2016[31] Fair	NR	Not able to calculate	NR	0.24 (0.16 to 0.36)	NR	NR	NR
Morgat, 2016[31] Fair	NR	0.40 (0.14 to 1.18)	NR	1.60 (0.60 to 4.29)	NR	NR	NR
Morgat, 2016[31] Fair	NR	1.20 (0.44 to 3.25)	NR	0.80 (0.29 to 2.22)	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Putzer, 2009[32] Fair	^{68}Ga-DOTATOC	PET	Clear demarcation of the lesion, with tracer accumulation higher than that in the liver and higher than physiologic activity.	PET or SPECT bone scintigraphy with PET or MRI for discordant results; follow-up control imaging within 6 months in ~60% of patients	Retrospective	Austria Department of Nuclear Medicine
Putzer, 2009[32] Fair	Not applicable	CT	Same as above	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{68}Ga-DOTATATE	PET/CT	Unclear	Multidisciplinary team consensus using all imaging modalities and clinical information.	Prospective cross-sectional	USA

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Putzer, 2009[32] Fair	Patients with histologically confirmed NETs	Age range (years): 32-87 Female: 43% Primary site: -Stomach: 6% -Small bowel: 29% -Colon: 6% -Rectum: 4% -Anal region: 2% -Pancreas: 22% -Prostate gland: 2% -Bronchial carcinoid: 10% -Unknown: 20%	N=51 66%	Detection of bone metastases, per-patient analysis	37	1	1	12	97%
Putzer, 2009[32] Fair	Same as above	Same as above	Same as above	Detection of bone metastases, per-patient analysis	22	0	16	13	58%
Sadowski, 2016[33] Poor	Nonpregnant patients ≥18 years old, suspected or known to have GEP NETs on imaging (CT, MRI, ^{18}F-FDG PET) and/or biochemical evidence of GEP NETs, and/or a familial predisposition to NET (MEN1 or von Hippel-Lindau).	Age (mean, years): 51; range: 19-82 Female: 56% Patients with symptoms: 55% Chromogranin A (median, ng/mL): 87.5; range: 20-18,710 Previous surgery: 77.5% -Pancreatic NET: 44.9% -Gastro-enteric NET: 55.1% Prior proven NET -Pancreatic: 27.5% -Small/large bowel: 23.7%/3.0% -Insulinoma: 5.3% -Gastic: 5.3% -Thymic carcinoid: 0.8% -Vipoma: 1.5% -Lung: 0.8%	N=131 82%	Detection of gastro-entero-pancreatic NETs, per-lesion analysis	847	NR	44	NR	95.1% (92.4 to 96.8)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Putzer, 2009[32] Fair	97.37% (86.19 to 99.93)	92%	92.31% (63.97 to 99.81)	NR	97.37% (84.90 to 99.59)	NR	92.31% (63.29 to 98.82)
Putzer, 2009[32] Fair	57.89% (40.82 to 73.69)	100%	100% (75.29 to 100)	NR	100.00%	NR	44.83% (35.88 to 54.12)
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Putzer, 2009[32] Fair	NR	12.66 (1.92 to 83.27)	NR	0.03 (0.00 to 0.20)	NR	NR	NR
Putzer, 2009[32] Fair	NR	Unable to calculate	NR	0.42 (0.29 to 0.61)	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Sadowski, 2016[33] Poor	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	Not applicable	CT and/or MRI	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{68}Ga-DOTATATE	PET/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	Not applicable	CT and/or MRI	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{68}Ga-DOTATATE	PET/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	Not applicable	CT and/or MRI	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{68}Ga-DOTATATE	PET/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	Not applicable	CT and/or MRI	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{68}Ga-DOTATATE	PET/CT	Unclear	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs, per-lesion analysis	275	NR	44	NR	30.9% (25.0 to 37.5)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs, per-lesion analysis	404	NR	487	NR	45.3% (37.9 to 52.9)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the pancreas	105	NR	5	NR	95.5% (89.4 to 98.1)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the pancreas	22	NR	88	NR	20% (12.8 to 29.8)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the pancreas	59	NR	51	NR	53.6% (42.8 to 64.2)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the liver	396	NR	12	NR	97.1% (93.7 to 98.7)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the liver	170	NR	238	NR	41.7% (31.1 to 53.1)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the liver	233	NR	175	NR	57.1% (44.7 to 68.7)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bowel	49	NR	2	NR	96.1% (75.9 to 99.5)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bowel	7	NR	44	NR	13.7% (5.4 to 30.7)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bowel	6	NR	45	NR	11.8% (3.6 to 32.6)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the lung and mediastinum	30	NR	10	NR	75% (54.4 to 88.3)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Sadowski, 2016[33] Poor	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	Not applicable	CT and/or MRI	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{68}Ga-DOTATATE	PET/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	Not applicable	CT and/or MRI	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{68}Ga-DOTATATE	PET/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	^{111}In-Pentetreotide	SPECT/CT	Unclear	Same as above	Same as above	Same as above
Sadowski, 2016[33] Poor	Not applicable	CT and/or MRI	Unclear	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the lung and mediastinum	16	NR	24	NR	40% (25.3 to 56.7)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the lung and mediastinum	30	NR	10	NR	75% (53.0 to 88.9)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the abdomen and retroperitoneal lymph node	144	NR	9	NR	94.1% (87.1 to 97.4)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the abdomen and retroperitoneal lymph node	41	NR	112	NR	26.8% (16.6 to 40.2)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the abdomen and retroperitoneal lymph node	60	NR	93	NR	39.2% (29.7 to 49.6)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bone	123	NR	6	NR	95.3% (82.5 to 98.9)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bone	19	NR	110	NR	14.7% (6.4 to 30.6)
Sadowski, 2016[33] Poor	Same as above	Same as above	Same as above	Detection of GEP NETs in the bone	16	NR	113	NR	12.4% (7.3 to 20.3)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Sadowski, 2016[33] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Sadowski, 2016[33] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET/CT	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Consensus decision based on correlation of all available image data, histologic, and surgical findings were available, and clinical follow-up of ≥12 months.	Prospective cohort	Germany
Schraml, 2013[34] Fair	Not applicable	MRI	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	CT	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Schraml, 2013[34] Fair	Patients with histologically proven NET and suspicion of metastatic spread.	Age (mean, years): 57 Female: 49% Primary tumor site: -Gastroenteropancreatic syste: 63% -Thyroid: 4% -Bronchopulmonary system: 4% -Thymus: 4% -Cervix: 4% -Parotid gland: 2% -Cranium: 2% -Adrenal gland: 2% -Unknown: 15%	N=51 80% (41/51)	Detection of metastatic disease, per-patient analysis	40	0	1	10	98% (87 to 100)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease, per-patient analysis	40	1	1	9	98% (87 to 100)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease, per-patient analysis	36	1	5	9	88% (74 to 96)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease, per-patient analysis	37	1	4	9	90% (77 to 97)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Schraml, 2013[34] Fair	97.56% (87.14 to 99.94)	100% (69 to 100)	100% (69.15 to 100)	NR	100.00%	NR	90.91% (59.06 to 98.58)
Schraml, 2013[34] Fair	97.56% (87.14 to 99.94)	90% (56 to 100)	90% (55.50 to 99.75)	NR	97.56% (86.16 to 99.61)	NR	90.00% (56.22 to 98.44)
Schraml, 2013[34] Fair	87.80% (73.80 to 95.92)	90% (56 to 100)	90.00% (55.50 to 99.75)	NR	97.30% (84.82 to 99.57)	NR	64.29% (43.56 to 80.76)
Schraml, 2013[34] Fair	90.24% (76.87 to 97.28)	90% (56 to 100)	90.00% (55.50 to 99.75)	NR	97.37% (85.18 to 99.58)	NR	69.23% (46.44 to 85.38)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Schraml, 2013[34] Fair	NR	Unable to calculate	NR	0.02 (0.00 to 0.17)	NR	NR	98% (90 to 100)
Schraml, 2013[34] Fair	NR	9.76 (1.52 to 62.67)	NR	0.03 (0.00 to 0.19)	NR	NR	96% (87 to 100)s
Schraml, 2013[34] Fair	NR	8.78 (1.36 to 56.57)	NR	0.14 (0.06 to 0.32)	NR	NR	88% (76 to 96)
Schraml, 2013[34] Fair	NR	9.02 (1.40 to 58.09)	NR	0.11 (0.04 to 0.28)	NR	NR	90% (76 to 96

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET/CT	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	MRI	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	CT	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET/CT	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease, per-lesion analysis	545	7	48	10	92% (89 to 94)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease, per-lesion analysis	540	53	53	9	91% (88 to 93)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease, per-lesion analysis	381	9	212	9	64% (60 to 68)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease, per-lesion analysis	481	43	111	9	81% (78 to 84)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lungs, per-lesion analysis	54	0	0	-	100% (93 to 100)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Schraml, 2013[34] Fair	91.19% (89.41 to 93.97)	NR	58.82% (32.92 to 81.56)	NR	98.73% (97.78 to 99.28)	NR	17.24% (11.41 to 25.21)
Schraml, 2013[34] Fair	91.06% (88.47 to 93.23)	NR	14.52% (6.86 to 25.78)	NR	91.06% (90.16 to 91.89)	NR	14.52% (8.10 to 24.66)
Schraml, 2013[34] Fair	64.25% (60.24 to 68.11)	NR	50% (26.02 to 73.98)	NR	97.69% (96.37 to 98.54)	NR	4.07% (2.57 to 6.39)
Schraml, 2013[34] Fair	81.25% (77.87 to 84.32)	NR	17.31% (8.23 to 30.33)	NR	81.79% (90.76 to 92.72)	NR	7.50% (4.19 to 13.07)
Schraml, 2013[34] Fair	100% (93.40 to 100.00)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Schraml, 2013[34] Fair	NR	2.23 (1.26 to 3.94)	NR	0.14 (0.09 to 0.22)	NR	NR	NR
Schraml, 2013[34] Fair	NR	1.07 (0.96 to 1.18)	NR	0.62 (0.32 to 1.19)	NR	NR	NR
Schraml, 2013[34] Fair	NR	1.28 (0.81 to 2.05)	NR	0.72 (0.44 to 1.15)	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.98 (0.86 to 1.12)	NR	0.98 (0.86 to 1.12)	NR	NR	NR
Schraml, 2013[34] Fair	NR	1	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Schraml, 2013[34] Fair	Not applicable	MRI	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	CT	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET/CT	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	MRI	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion.	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lungs, per-lesion analysis	47	1	7	-	87% (75 to 95)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lungs, per-lesion analysis	4	1	50	-	7% (2 to 18)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lungs, per-lesion analysis	54	0	0	-	100% (93 to 100)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the liver, per-lesion analysis	245	0	21	-	92% (88 to 95)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the liver, per-lesion analysis	264	11	2	-	99% (97 to 99)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the liver, per-lesion analysis	169	0	97	-	64% (57 to 69)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Schraml, 2013[34] Fair	87.04% (75.10 to 94.63)	NR	Unable to calculate	NR	97.92% (97.70 to 98.12)	NR	Unable to calculate
Schraml, 2013[34] Fair	7.41% (2.06 to 17.89)	NR	Unable to calculate	NR	80.00% (60.90 to 91.13)	NR	Unable to calculate
Schraml, 2013[34] Fair	100% (93.40 to 100.00)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate
Schraml, 2013[34] Fair	92.11% (88.19 to 95.05)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate
Schraml, 2013[34] Fair	99.25% (97.31 to 99.91)	NR	Unable to calculate	NR	96.00% (95.96 to 96.04)	NR	Unable to calculate
Schraml, 2013[34] Fair	63.53% (57.44 to 69.33)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Schraml, 2013[34] Fair	NR	0.7 (0.79 to 0.96)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.07 (0.03 to 0.19)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	1	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.92	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.99 (0.98 to 1.00)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.64	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Schraml, 2013[34] Fair	Not applicable	CT	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET/CT	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	MRI	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	CT	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the liver, per-lesion analysis	226	3	40	-	85% (80 to 89)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the bones, per-lesion analysis	108	0	23	-	82% (75 to 89)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the bones, per-lesion analysis	126	2	5	-	96% (91 to 99)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the bones, per-lesion analysis	90	0	41	-	69% (60 to 77)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the bones, per-lesion analysis	81	0	50	-	62% (53 to 70)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Schraml, 2013[34] Fair	84.96% (80.09 to 89.03)	NR	Unable to calculate	NR	98.69% (98.62 to 98.75)	NR	Unable to calculate
Schraml, 2013[34] Fair	82.44% (74.83 to 88.53)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate
Schraml, 2013[34] Fair	96.18% (91.32 to 98.75)	NR	Unable to calculate	NR	98.44% (98.38 to 98.49)	NR	Unable to calculate
Schraml, 2013[34] Fair	68.70% (60.02 to 76.52)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate
Schraml, 2013[34] Fair	61.83% (52.94 to 70.18)	NR	Unable to calculate	NR	100.00%	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Schraml, 2013[34] Fair	NR	0.85 (0.81 to 0.89)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.82	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.96 (0.93 to 1.00)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.69	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.62	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET/CT	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	MRI	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	CT	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET/CT	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lymph nodes, per-lesion analysis	99	4	0	-	100% (96 to 100)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lymph nodes, per-lesion analysis	72	34	27	-	73% (63 to 81)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lymph nodes, per-lesion analysis	96	3	3	-	97% (91 to 99)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in the lymph nodes, per-lesion analysis	87	38	12	-	88% (80 to 94)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in other organs, per-lesion analysis	39	3	4	-	91% (78 to 97)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Schraml, 2013[34] Fair	100% (96.34 to 100.00)	NR	Unable to calculate	NR	96.12% (96.12 to 96.12)	NR	Unable to calculate
Schraml, 2013[34] Fair	72.73% (62.85 to 81.20)	NR	Unable to calculate	NR	67.92% (65.24 to 70.49)	NR	Unable to calculate
Schraml, 2013[34] Fair	96.97% (91.40 to 99.37)	NR	Unable to calculate	NR	96.97% (96.87 to 97.07)	NR	Unable to calculate
Schraml, 2013[34] Fair	87.88% (79.78 to 93.58)	NR	Unable to calculate	NR	69.60% (68.03 to 71.13)	NR	Unable to calculate
Schraml, 2013[34] Fair	90.70% (77.86 to 97.41)	NR	Unable to calculate	NR	92.86% (92.20 to 93.47)	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Schraml, 2013[34] Fair	NR	1 (1 to 1)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.73 (0.64 to 0.82)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.97 (0.94 to 1.00)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.88 (0.82 to 0.95)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.91 (0.82 to 1.00)	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Schraml, 2013[34] Fair	Not applicable	MRI	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	^{68}Ga-DOTATOC	PET	In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion.	Same as above	Same as above	Same as above
Schraml, 2013[34] Fair	Not applicable	CT	Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Same as above	Same as above	Same as above
Schreiter, 2012[35] Fair	^{68}Ga-DOTATOC	PET/CT	Readers rated lesions on 3-point scale (1=benign; 2=indifferent; 3=malignant), those rated 3 were considered positive.	Histopathology, follow-up examinations (mean follow-up was 29 months; range was 7-72 months).	Prospective cohort	Unclear
Schreiter, 2012[35] Fair	Not applicable	MRI	Same as above	Same as above	Same as above	Same as above
Schreiter, 2012[35] Fair	Not applicable	CT	Same as above	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in other organs, per-lesion analysis	31	5	12	-	72% (56 to 85)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in other organs, per-lesion analysis	22	5	21	-	51% (36 to 67)
Schraml, 2013[34] Fair	Same as above	Same as above	Same as above	Detection of metastatic disease in other organs, per-lesion analysis	33	2	9	-	79% (61 to 88)
Schreiter, 2012[35] Fair	Patients with biopsy proven NET scheduled for ^{68}Ga-DOTATOC PET/CT because of known or suspected liver metastases on the basis of other imaging results. Patients were excluded due to inadequate contrast enhancement in the liver during multiphase PET/CT, and claustrophobia with discontinuation of the MRI examination.	Age (mean, years): 54.8; range: 34-73 Female: 41% Primary tumors: -Pancreas: 46% -Ileum: 23% -Stomach: 9% -Duodenum: 9% -Rectum: 5% -Lungs: 5% -Unknown: 5%	N=22 NR	Differentiation of liver metastases from NET lesions, per-lesion analysis	NR	NR	NR	NR	73.5% (64.3 to 81.3)
Schreiter, 2012[35] Fair	Same as above	Same as above	Same as above	Differentiation of liver metastases from NET lesions, per-lesion analysis	NR	NR	NR	NR	87.6% (80.1 to 93.1)
Schreiter, 2012[35] Fair	Same as above	Same as above	Same as above	Differentiation of liver metastases from NET lesions, per-lesion analysis	NR	NR	NR	NR	68.1% (58.7 to 76.6)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Schraml, 2013[34] Fair	72.09% (56.33 to 84.67)	NR	Unable to calculate	NR	86.11% (83.73 to 88.19)	NR	Unable to calculate
Schraml, 2013[34] Fair	51.16% (35.46 to 66.69)	NR	Unable to calculate	NR	81.48% (76.67 to 85.49)	NR	Unable to calculate
Schraml, 2013[34] Fair	78.57% (63.19 to 89.70)	NR	Unable to calculate	NR	94.29% (93.37 to 95.08)	NR	Unable to calculate
Schreiter, 2012[35] Fair	Unable to calculate	88.2% (78.6 to 99.1)	Unable to calculate	93.4% (87.4 to 97.1)	Unable to calculate	69.4% (59.3 to 78.3)	Unable to calculate
Schreiter, 2012[35] Fair	Unable to calculate	86.8% (76.4 to 93.8)	Unable to calculate	92.6% (86.5 to 96.6)	Unable to calculate	82.9% (73 to 90.3)	Unable to calculate
Schreiter, 2012[35] Fair	Unable to calculate	85.3% (74.6 to 92.7)	Unable to calculate	91.9% (85.6 to 96)	Unable to calculate	65.4% (55.4 to 74.4)	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Schraml, 2013[34] Fair	NR	0.72 (0.60 to 0.87)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.51 (0.38 to 0.69)	NR	Unable to calculate	NR	NR	NR
Schraml, 2013[34] Fair	NR	0.79 (0.67 to 0.92)	NR	Unable to calculate	NR	NR	NR
Schreiter, 2012[35] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Schreiter, 2012[35] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Schreiter, 2012[35] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Schreiter, 2012[35] Fair	^{68}Ga-DOTATOC	PET	Same as above	Same as above	Same as above	Same as above
Schreiter, 2012[35] Fair	^{68}Ga-DOTATOC	PET-MRI	Same as above	Same as above	Same as above	Same as above
Van Binnebeek, 2016[36] Poor	^{68}Ga-DOTATOC	PET/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Mainteance of lesions on follow-up scans.	Prospective trial	Belgium University hospital
Van Binnebeek, 2016[36] Poor	^{111}In-Pentetreotide	SPECT/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Same as above	Same as above	Same as above
Van Binnebeek, 2016[36] Poor	^{68}Ga-DOTATOC	PET/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Same as above	Same as above	Same as above
Van Binnebeek, 2016[36] Poor	^{111}In-Pentetreotide	SPECT/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Schreiter, 2012[35] Fair	Same as above	Same as above	Same as above	Differentiation of liver metastases from NET lesions, per-lesion analysis	NR	NR	NR	NR	53.1% (43.5 to 62.5)
Schreiter, 2012[35] Fair	Same as above	Same as above	Same as above	Differentiation of liver metastases from NET lesions, per-lesion analysis	NR	NR	NR	NR	91.2% (84.3 to 95.7)
Van Binnebeek, 2016[36] Poor	Patients with metastatic NET, enrolled in a prospective phase II monocentric trial.	Age (mean, years): 59; range: 31-80 Female: 57% Primary site -Gastroenteropancreatic: 74% -Lung: 7.5% -Merckel cell carcinomas: 3.9% -Breast: 1.8% -Kidney: 1.8% -Other/unknown: 11%	N=53 100%	Detection of metastatic NETs, per-lesion analysis	NR	NR	NR	NR	99.9% (99.3 to 100)
Van Binnebeek, 2016[36] Poor	Same as above	Same as above	Same as above	Detection of metastatic NETs, per-lesion analysis	NR	NR	NR	NR	60.1% (48.5 to 70.2)
Van Binnebeek, 2016[36] Poor	Same as above	Same as above	Same as above	Detection of metastatic NETs in liver	NR	NR	NR	NR	99.8% (99.3 to 100)
Van Binnebeek, 2016[36] Poor	Same as above	Same as above	Same as above	Detection of metastatic NETs in liver	NR	NR	NR	NR	66.5% (57.7 to 74.3)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Schreiter, 2012[35] Fair	Unable to calculate	79.4% (74.6 to 92.7)	Unable to calculate	89.0% (85.6 to 96)	Unable to calculate	56.2% (46.9 to 65.2)	Unable to calculate
Schreiter, 2012[35] Fair	Unable to calculate	95.6% (87.6 to 99.1)	Unable to calculate	97.4% (92.6 to 99.5)	Unable to calculate	87.2% (77.7 to 93.7)	Unable to calculate
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Schreiter, 2012[35] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Schreiter, 2012[35] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Van Binnebeek, 2016[36] Poor	^{68}Ga-DOTATOC	PET/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Same as above	Same as above	Same as above
Van Binnebeek, 2016[36] Poor	^{111}In-Pentetreotide	SPECT/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Same as above	Same as above	Same as above
Van Binnebeek, 2016[36] Poor	^{68}Ga-DOTATOC	PET/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Same as above	Same as above	Same as above
Van Binnebeek, 2016[36] Poor	^{111}In-Pentetreotide	SPECT/CT	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Same as above	Same as above	Same as above
Venkitaraman, 2014[37] Good	^{68}Ga-DOTATOC	PET/CT	PET was assessed for areas of increased radiotracer uptake. Corresponding areas in the CT images and fused PET/CT images were corroborated.	Biopsy	Prospective cohort	India Department of Surgical Disciplines

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Van Binnebeek, 2016[36] Poor	Same as above	Same as above	Same as above	Detection of metastatic NETs in bones	NR	NR	NR	NR	100%
Van Binnebeek, 2016[36] Poor	Same as above	Same as above	Same as above	Detection of metastatic NETs in bones	NR	NR	NR	NR	34.5% (18 to 55.9)
Van Binnebeek, 2016[36] Poor	Same as above	Same as above	Same as above	Detection of metastatic NETs in lymph nodes	NR	NR	NR	NR	100%
Van Binnebeek, 2016[36] Poor	Same as above	Same as above	Same as above	Detection of metastatic NETs in lymph nodes	NR	NR	NR	NR	70.5% (56.1 to 81.7)
Venkitaraman, 2014[37] Good	Patients with clinical suspicion of pulmonary carcinoid tumour based on history, examination, or radiological findings. Children <15 years, pregnant women, uncontrolled diabetes with blood sugar level of >140 mg/dl, and patients who refused to give consent for the study were excluded.	Age (mean, years): 34.22 (range: 16-71 Female: 53% Typical carcinoid: 66% Atypical carcinoid: 16% Mucoepidermoid carcinoma: 6% Adenoid cystic carcinoma: 3% Schwannoma: 3% Squamous cell carcinoma: 6%	N=32 100%	Detection of pulmonary carcinoids, per-patient analysis	25	0	1	6	96.15% (58.7 to 99.8)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Van Binnebeek, 2016[36] Poor	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Venkitaraman, 2014[37] Good	96.15% (80.36 to 99.90)	100% (59.1 to 100)	100% (54.07 to 100)	100% (71.5 to 100)	100.00%	85.71% (29.4 to 99.2)	85.71% (46.75 to 97.62)

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Van Binnebeek, 2016[36] Poor	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Venkitaraman, 2014[37] Good	NR	Unable to calculate	NR	0.04 (0.01 to 0.26)	NR	NR	97%

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Tracer	Imaging Test	Definition of a Positive Test	Reference Standard	Type of Study	Country Setting
Venkitaraman, 2014[37] Good	^{18}F-FDG	PET/CT	Same as above	Same as above	Same as above	Same as above
Versari, 2010[38] Fair	^{68}Ga-DOTATOC	PET/CT	Unclear	Lesions detected by any imaging technique, unambiguous cytologic and/or histologic findings; and 6 month follow-up for negative scans.	Retrospective	Italy Endocrinology Unit
Versari, 2010[38] Fair	Not applicable	MDCT	Same as above	Same as above	Same as above	Same as above
Versari, 2010[38] Fair	^{68}Ga-DOTATOC	PET/CT	Same as above	Same as above	Same as above	Same as above
Versari, 2010[38] Fair	Not applicable	MDCT	Same as above	Same as above	Same as above	Same as above

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Inclusion Criteria	Population Characteristics	Sample Size Proportion With Condition	Analysis Method	TP	FP	FN	TN	Reported Sensitivity (95% CI)
Venkitaraman, 2014[37] Good	Same as above	Same as above	Same as above	Detection of pulmonary carcinoids, per-patient analysis	18	5	8	1	78.26% (46.2 to 94.9)
Versari, 2010[38] Fair	Patients who consecutively underwent both EUS and ^{68}GA-DOTATOC PET at the author's institution between March 2007 and November 2008 for the suspicion of NET in the duodenopancreatic area.	Age (mean, years): 56; range: 21-80 Female: 42%	N=19 100%	Detection of duodenopancreatic NETs, per-lesion analysis	22	1	4	5	87%
Versari, 2010[38] Fair	Same as above	Same as above	N=16 100%	Detection of duodenopancreatic NETs, per-lesion analysis	16	1	6	4	72%
Versari, 2010[38] Fair	Same as above	Same as above	N=19 100%	Detection of duodenopancreatic NETs, per-patient analysis	13	NR	0	NR	NR
Versari, 2010[38] Fair	Same as above	Same as above	N=16 100%	Detection of duodenopancreatic NETs, per-patient analysis	10	NR	1	NR	NR

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Calculated Sensitivity (95% CI)	Reported Specificity (95% CI)	Calculated Specificity (95% CI)	Reported PPV (95% CI)	Calculated PPV (95% CI)	Reported NPV (95% CI)	Calculated NPV (95% CI)
Venkitaraman, 2014[37] Good	69.23% (48.21 to 85.67)	11.1% (3.4 to 47.5)	16.67% (0.42 to 64.12)	69.23% (42.1 to 85.2)	78.26% (69.86 to 84.83)	16.6% (6.4 to 61.5)	11.11% (1.87 to 45.03)
Versari, 2010[38] Fair	84.62% (65.13 to 95.64)	NR	83.33% (35.88 to 99.58)	NR	95.65% (78.49 to 99.25)	NR	55.56% (32.15 to 76.73)
Versari, 2010[38] Fair	72.73% (49.78 to 89.27)	NR	80% (28.36 to 99.49)	NR	94.12% (73.12 to 98.95)	NR	40% (22.86 to 60)
Versari, 2010[38] Fair	100.00%	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate
Versari, 2010[38] Fair	90.90%	NR	Unable to calculate	NR	Unable to calculate	NR	Unable to calculate

Table 4a. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Reported AUROC	Calculated PLR (95% CI)	Reported PLR (95% CI)	Calculated NLR (95% CI)	Reported NLR (95% CI)	Other Measures of Diagnostic Accuracy	Imaging Accuracy
Venkitaraman, 2014[37] Good	NR	0.83 (0.53 to 1.29)	NR	1.85 (0.28 to 12.10)	NR	NR	59.37%
Versari, 2010[38] Fair	NR	5.08 (0.84 to 30.61)	NR	0.18 (0.07 to 0.49)	NR	NR	NR
Versari, 2010[38] Fair	NR	3.64 (0.62 to 21.38)	NR	0.34 (0.15 to 0.77)	NR	NR	NR
Versari, 2010[38] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR
Versari, 2010[38] Fair	NR	Unable to calculate	NR	Unable to calculate	NR	NR	NR

Abbreviations: CE= contrast enhanced; CI=confidence interval; CT= computed tomography; EUS= endoscopic ultrasound; F= fluorine; FDG= fluorodeoxyglucose; Ga= Gallium; GEPNET= gastroenteropancreatic neuroendocrine tumor; HYNIC= hydrazinonicotinyl-Tyr3; In= indium; MBq; megabecquerel; MDCT= multidetector computed tomography; MCC= major complications or comorbidities; MEN= multiple endocrine neoplasia; MEN1= Multiple endocrine neoplasia type 1; MRI= magnetic resonance imaging; NET= neuroendocrine tumor; NLR=negative liklihood ratio; NPV=negative predictive value; NR= not reported; PET= positron emission tomography; PLR=positive liklihood ratio; PPV=positive predictive value; SPECT= single photon emission computed tomography; SSTR-PET= somatostatin receptor positron emission tomography.

Table 4b. Summarized Characteristics of Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Imaging Test	N	Mean Age (years)	Female	Primary Tumor Site or NET Location	Definition of a Positive Test	Reference Standard
Deppen, 2016[24] Fair	A: ^{68}Ga-DOTATATE PET/CT B: ^{111}In-Pentetreotide SPECT or SPECT/CT	97	53.7	58%	Various NETs: -Midgut carcinoid: 45% -GEP: 23% -Unknown primary: 12% -Symptoms only: 7% -Pulmonary: 7% -Hindgut or rectal: 3% -Other: 2%	Unclear	Single or multiple CT or MRI scans, surgical tissue confirmation, or combination thereof.
Etchebehere, 2014[25] Fair	A: ^{68}Ga-DOTATATE PET/CT B: 111-185 MBq (3-5 mCi) of 99mTc-HYNIC-octreotide SPECT/CT C: MRI	19	54.3	47%	Various NETs, primary site: -Bronchi: 22% -Pancreas: 31% -Gut: 31%	A: Intense focal uptake in comparision to the adjacent tissues was seen in the coronal, transaxial, and sagittal views. B: Intense focal uptake in comparision to the adjacent tissues was seen in the coronal, transaxial, and sagittal views. C: Analzyed in terms of number, size, location, and signal intensity and were compared with the T1-weighted and short-τ inversion recovery sequences to rule out false-positive findings. Lymph nodes were defined as malignant according to the diameter of the small axis.	Consensus among investigators at the end of the study evaluating all lesions by all methods, clinical follow-up, and biopsy of suggestive lesions when possible.
Froeling, 2012[26] Fair	A: ^{68}Ga-DOTATOC PET B: ^{68}Ga-DOTATOC PET/CT C: CT	21	41.4	48%	Various NETs; all patients had MEN1 syndrome	Blinded radiologists and nuclear medicine physicians analyzed PET and CT separately first, then PET/CT. Lesions were characterized on a 3-point scale: non-MEN-associated lesions, equivocal lesions, MEN-associated lesions.	Histopathologic proof or confirmed by clinical and radiologic follow-up.

Table 4b. Summarized Characteristics of Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Imaging Test	N	Mean Age (years)	Female	Primary Tumor Site or NET Location	Definition of a Positive Test	Reference Standard
Gabriel, 2007[27] Good	A: ^{68}Ga-DOTATOC PET B: CT	84	58.2	43%	Various NETs (details not reported)	A: Clearly demarked findings with higher tracer uptake compared with liver uptake, tracer accumulation in structures that did not take up tracer physiologically or was higher than background activity, or pancreatic head: irregular or protrusive shape of finding; clear delineation fro madjacent tissue with higher uptake than liver uptake. B: Specific appearance of malignant disease derived from NET.	Histological confirmation and repeated clinical examinations with CT or MRI after 3 or 6 months for positive findings and follow-up imaging after 6 months for negative scans.
Has Simsek, 2014[28] Poor	A: ^{68}Ga-DOTATATE PET/CT B: ^{18}F-FDG PET/CT	27	56	63%	GEP NET: 100%	Significant accumulation of the tracer based on cisual assessment	Histology.
Kumar, 2011[29] Poor	A: ^{68}Ga-DOTATOC PET/CT B: ^{18}F-FDG PET/CT C: Contrast enhanced CT	20	42.5*	50%	Pancreatic NET: 100%	A: Any non physiological uptake more than surrounding tissue. B: Any non physiological focal area of increased ^{18}F-FDG uptake was looked for, keeping physiological tracer distribution in perspective. C: Assessed by experienecd radiologists for evidnce of primary/metastatic disease.	Biopsy/histopathology
Lococo, 2015[30] Poor	A: ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE or ^{68}Ga-DOTANOC PET/CT B: ^{18}F-FDG PET/CT	33	59.7	64%	Pulmonary carcinoid: -Stage I: 49% -Stage II: 36% -Stage III/IV: 15%	Any focal accumulation of each tracer in the lung nodule higher than the surrounding uptake.	Histological diagnosis.
Morgat, 2016[31] Fair	A: ^{68}Ga-DOTATOC PET/CT B: ^{111}In-Pentetreotide SPECT/CT C: 2 ml/kg iohexol contrast media CE-CT	19	47	63%	Duodenopancreatic NETs (all patients had MEN1): 100%	A: Focally increased uptake, compared with that of the surrounding tissue. B: Increased uptake was assessed by comparison with uptake by liver tissue, according to the European Assocation of Nuclear Medicine recommendations. C: Radiologist's blinded reading	Combination of unblinded analysis of the CE-CT with complementary investigations (MRI, EUS, ^{18}F-FDG PET, or histology, performed on an individual basis) results.

Table 4b. Summarized Characteristics of Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Imaging Test	N	Mean Age (years)	Female	Primary Tumor Site or NET Location	Definition of a Positive Test	Reference Standard
Putzer, 2009[32] Fair	A: ^{68}Ga-DOTATOC PET B: CT	51	Range: 32-87	43%	Various NETs Primary site: -Stomach: 6% -Small bowel: 29% -Colon: 6% -Rectum: 4% -Anal region: 2% -Pancreas: 22% -Prostate gland: 2% -Bronchial carcinoid: 10% -Unknown: 20%	Clear demarcation of the lesion, with tracer accumulation higher than that in the liver and higher than physiologic activity.	PET or SPECT bone scintigraphy with PET or MRI for discordant results; follow-up control imaging within 6 months in ~60% of patients
Sadowski, 2016[33] Poor	A: ^{68}Ga-DOTATATE PET/CT B: ^{111}In-Pentetreotide SPECT/CT C: CT and/or MRI	131	51	56%	Focus on identificatoin of unknown primary GEP or metastatic NETs GEP NETs -Pancreatic: 27.5% -Small/large bowel: 23.7%/3.0% -Insulinoma: 5.3% -Gastic: 5.3% -Thymic carcinoid: 0.8% -VIPoma: 1.5% -Lung: 0.8%	Unclear	Multidisciplinary team consensus using all imaging modalities and clinical information.

Table 4b. Summarized Characteristics of Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Imaging Test	N	Mean Age (years)	Female	Primary Tumor Site or NET Location	Definition of a Positive Test	Reference Standard
Schraml, 2013[34] Fair	A: ^{68}Ga-DOTATOC PET/CT B: MRI C: ^{68}Ga-DOTATOC PET D: CT	51	57	49%	Various NETs Primary site: -GEP system: 63% -Thyroid: 4% -Bronchopulmonary system: 4% -Thymus: 4% -Cervix: 4% -Parotid gland: 2% -Cranium: 2% -Adrenal gland: 2% -Unknown: 15%	A: In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics. B: Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics. C: In PET images, focul uptake exceeding normal regional tracer accumulation was classified as a malginant lesion. D: Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characterisics.	Consensus decision based on correlation of all available image data, histologic, and surgical findings were available, and clinical follow-up of ≥12 months.
Schreiter, 2012[35] Fair	A: ^{68}Ga-DOTATOC PET/CT B: MRI C: CT D: ^{68}Ga-DOTATOC PET E: ^{68}Ga-DOTATOC PET-MRI	22	54.8	41%	NETs with metastatic disease Primary tumors: -Pancreas: 46% -Ileum: 23% -Stomach: 9% -Duodenum: 9% -Rectum: 5% -Lungs: 5% -Unknown: 5%	Readers rated lesions on 3-point scale (1=benign; 2=indifferent; 3=malignant), those rated 3 were considered positive.	Histopathology, follow-up examinations (mean follow-up was 29 months; range was 7-72 months).

Table 4b. Summarized Characteristics of Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, year Quality	Imaging Test	N	Mean Age (years)	Female	Primary Tumor Site or NET Location	Definition of a Positive Test	Reference Standard
Van Binnebeek, 2016[36] Poor	A: ^{68}Ga-DOTATOC PET/CT B: ^{111}In-Pentetreotide SPECT/CT	53	59	57%	Various NETs, primary site (all had metastatic disease): -GEP: 74% -Lung: 7.5% -Merckel cell carcinomas: 3.9% -Breast: 1.8% -Kidney: 1.8% -Other/unknown: 11%	A focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake.	Mainteance of lesions on follow-up scans.
Venkitaraman, 2014[37] Good	A: ^{68}Ga-DOTATOC PET/CT B: ^{18}F-FDG PET/CT	32	34.22	53%	Pulmonary tumors: -Typical carcinoid: 66% -Atypical carcinoid: 16% -Mucoepidermoid carcinoma: 6% -Adenoid cystic carcinoma: 3% -Schwannoma: 3% -Squamous cell carcinoma: 6%	PET was assessed for areas of increased radiotracer uptake. Corresponding areas in the CT images and fused PET/CT images were corroborated.	Biopsy
Versari, 2010[38] Fair	A: ^{68}Ga-DOTATOC PET/CT B: MDCT	19	56	42%	Duodenopancreatic NETs: 100%	Unclear	Lesions detected by any imaging technique, unambiguous cytologic and/or histologic findings; and 6 month follow-up for negative scans.

*Values are median

Abbreviations: CE= contrast enhanced; CT= computed tomography; EUS= endoscopic ultrasound; F= fluorine; FDG= fluorodeoxyglucose; Ga= Gallium; GEP= gastroenteropancreatic; HYNIC= hydrazinonicotinyl-Tyr3; In= indium; MBq; megabecquerel; MDCT= multidetector computed tomography; MEN= multiple endocrine neoplasia; MEN1= Multiple endocrine neoplasia type 1; MRI= magnetic resonance imaging; NET= neuroendocrine tumor; PET= positron emission tomography; SPECT= single photon emission computed tomography.

Table 4c. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, Year Quality	Imaging Test	Analysis Method	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)	Imaging Accuracy
SSTR-PET vs. OctreoScan									
Detection of NETs									
Deppen, 2016[24] Fair	A: ^{68}Ga-DOTATATE PET/CT B: ^{111}In-Pentetreotide SPECT or SPECT/CT	Detection of cancer or progression, all types, per-patient analysis, only those who underwent SPECT/CT	A: 96.55% (82.24 to 99.91)* B: 82.76% (64.23 to 94.15)	A: 94.74% (73.97 to 99.87))* B: 94.74% (73.97 to 99.87)*	A: 96.55% (80.58 to 99.47))* B: 96% (77.96 to 99.39)*	A: 94.74% (72.34 to 99.20)* B: 78.26% (61.69 to 88.95)*	A: 18.34 (2.72 to 123.76)* B: 15.72 (2.32 to 106.71)*	A: 0.04 (0.01 to 0.25)* B: 0.18 (0.08 to 0.41)*	0.94 (0.89 to 1.00)
Etchebehere, 2014[25] Fair	A: ^{68}Ga-DOTATATE PET/CT B: 111-185 MBq (3-5 mCi) of 99mTc-HYNIC-octreotide SPECT/CT	Detection of NETs, per-lesion analysis	A: 96% B: 60%	A: 97% B: 99%	A: 94% B: 96%	A: 98% B: 83%	Unable to calculate	Unable to calculate	A: 97% B: 86%
Detection of GEP NETs									
Morgat, 2016[31] Fair	A: ^{68}Ga-DOTATOC PET/CT B: ^{111}In-Pentetreotide SPECT/CT	Detection of dpNETs, per-lesion analysis	A: 76% (64.75 to 85.11)* B: 20% (11.65 to 30.83)*	A: 100% (39.76 to 100)* B: 50% (6.76 to 93.24)*	A: 100%* B: 88.24% (71.82 to 95.67)*	A: 18.18% (12.93 to 24.95)* B: 3.23% (1.23 to 8.21)*	A: Unable to calculate B: 0.40 (0.14 to 1.18)*	A: 0.24 (0.16 to 0.36)* B: 1.60 (0.60 to 4.29)*	NR
Detection of Unknown Primary or Metastatic NETs									
Sadowski, 2016[33] Poor	A: ^{68}Ga-DOTATATE PET/CT B: ^{111}In-Pentetreotide SPECT/CT	Detection of GEP NETs, per-lesion analysis	A: 95.1% (92.4 to 96.8) B: 30.9% (25.0 to 37.5)	NR	Unable to calculate	Unable to calculate	Unable to calculate	Unable to calculate	NR
Detection of metastatic disease									
Van Binnebeek, 2016[36] Poor	A: ^{68}Ga-DOTATOC PET/CT B: ^{111}In-Pentetreotide SPECT/CT	Detection of NETs, per-lesion analysis	A: 99.9% (99.3 to 100) B: 60.1% (48.5 to 70.2)	NR	Unable to calculate	Unable to calculate	Unable to calculate	Unable to calculate	NR
SSTR-PET vs. ^{18}FDG-PET									
Detection of GEP NETs									
Has Simsek, 2014[28] Poor	A: ^{68}Ga-DOTATATE PET/CT B: ^{18}F-FDG PET/CT	Detection of GEP NETs overall, per-lesion analysis	A: 95% (NR) B: 37% (NR)	NR	A: 93.8% (NR) B: 36.2% (NR)	Unable to calculate	Unable to calculate	Unable to calculate	NR
Kumar, 2011[29] Poor	A: ^{68}Ga-DOTATOC PET/CT B: ^{18}F-FDG PET/CT	Detection of primary NETs, per-patient analysis	A: 100% (83.16 to 100)* B: 25% (3.19 to 65.09)*	NR	A: 100% (83.16 to 100)* B: 100% (63.06 to 100)*	Unable to calculate	A: 1* B: 0.25*	Unable to calculate	NR

Table 4c. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, Year Quality	Imaging Test	Analysis Method	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)	Imaging Accuracy
Detection of Pulmonary Carcinoids									
Lococo, 2015[30] Poor	A: ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE or ^{68}Ga-DOTANOC PET/CT B: ^{18}F-FDG PET/CT	Detection of pulmonary carcinoids, per-patient analysis	A: 78.79% (61.09 to 91.02)* B: 54.55% (36.35 to 71.89)*	NR	A: 100%* B: 100% (89.42 to 100)*	Unable to calculate	A: 0.79* B: 0.55*	Unable to calculate	NR
Venkitaraman, 2014[37] Fair	A: ^{68}Ga-DOTATOC PET/CT B: ^{18}F-FDG PET/CT	Detection of pulmonary carcinoids, per-patient analysis	A: 96.15% (80.36 to 99.90)* B: 69.23% (48.21 to 85.67)*	A: 100% (54.07 to 100)* B: 16.67% (0.42 to 64.12)*	A: 100% (71.5 to 100)* B: 78.26% (69.86 to 84.83)*	A: 85.71% (46.75 to 97.62)* B: 11.11% (1.87 to 45.03)*	A: Unable to calculate B: 0.83 (0.53 to 1.29)*	A: 0.04 (0.01 to 0.26)* B: 1.85 (0.28 to 12.10)*	A: 96.87% B: 59.37%
Detection of Metastatic Disease									
Kumar, 2011[29] Poor	A: ^{68}Ga-DOTATOC PET/CT B: ^{18}F-FDG PET/CT	Detection of metastatic disease, per-patient analysis	A: 92.8% (66 to 98.8) B: 20% (3.1 to 55.5)	A: 100% (54 to 100) B: 100% (16.5 to 100)	A: 100% (75.1 to 100) B: 100% (19.2 to 100)	A: 85.7% (42.2 to 97.6)* B: 11.1% (1.8 to 48.2)*	Unable to calculate	Unable to calculate	NR
SSTR-PET vs. CT/MRI									
Detection of NETs									
Etchebehere, 2014[25] Fair	A: ^{68}Ga-DOTATATE PET/CT B: MRI	Detection of NETs, per-lesion analysis	A: 96% B: 72%	A: 97% B: 100%	A: 94% B: 100%	A: 98% B: 88%	Unable to calculate	Unable to calculate	A: 97% B: 91%
Gabriel, 2007[27] Good	A: ^{68}Ga-DOTATOC PET B: CT	Detection of NETs, per-patient analysis	A: 97.18% (90.19 to 99.66)* B: 61.19% (48.50 to 72.86)*	A: 92.31% (63.97 to 99.81)* B: 70.59% (44.04 to 89.69)*	A: 98.57% (91.30 to 99.78)* B: 89.13% (79.30 to 94.61)*	A: 85.71% (60.26 to 95.96)* B: 31.58% (23.10 to 41.49)*	A: 12.63 (1.92 to 83.09)* B: 2.08 (0.97 to 4.45)*	A: 0.03 (0.01 to 0.12)* B: 0.55 (0.36 to 0.84)*	A: 96% B: 63%
Detection of GEP NETs									
Froeling, 2012[26] Fair	A: ^{68}Ga-DOTATOC PET B: ^{68}Ga-DOTATOC PET/CT C: CT	Detection of NET lesions	A: 85% (NR) B: 91.7% (NR) C: 43.3% (NR)	A: 96.8% (NR) B: 93.5% (NR) C: 61.3% (NR)	Unable to calculate	Unable to calculate	Unable to calculate	Unable to calculate	NR
Kumar, 2011[29] Poor	A: ^{68}Ga-DOTATOC PET/CT B: Contrast enhanced CT	Detection of primary NETs, per-patient analysis	A: 100% (83.16 to 100)* B: 84.21% (60.42 to 96.62)*	A: NR B: 0% (0 to 84.19)*	A: 100% (83.16 to 100)* B: 88.89% (86.82 to 90.67)*	Unable to calculate	A: 1* B: 0.84 (0.69 to 1.02)*	Unable to calculate	NR

Table 4c. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, Year Quality	Imaging Test	Analysis Method	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)	Imaging Accuracy
Morgat, 2016[31] Fair	A: ^{68}Ga-DOTATOC PET/CT B: 2 ml/kg iohexol contrast media CE-CT	Detection of dpNETs, per-lesion analysis	A: 76% (64.75 to 85.11)* B: 60% (48.04 to 71.15)*	A: 100% (39.76 to 100)* B: 50% (6.76 to 93.24)*	A: 100%* B: 95.74% (89.25 to 98.39)*	A: 18.18% (12.93 to 24.95)* B: 6.25% (2.35 to 15.58)*	A: Unable to calculate B: 1.20 (0.44 to 3.25)*	A: 0.24 (0.16 to 0.36)* B: 0.80 (0.29 to 2.22)*	NR
Versari, 2010[38] Fair	A: ^{68}Ga-DOTATOC PET/CT B: MDCT	Detection of GEP NETs, per-patient analysis	A: 100%* B: 90.9%*	NR	Unable to calculate	Unable to calculate	Unable to calculate	Unable to calculate	NR
Versari, 2010[38] Fair	A: ^{68}Ga-DOTATOC PET/CT B: MDCT	Detection of GEP NETs, per-lesion analysis	A: 84.62% (65.13 to 95.64)* B: 72.73% (49.78 to 89.27)*	A: 83.33% (35.88 to 99.58)* B: 80% (28.36 to 99.49)*	A: 95.65% (78.49 to 99.25)* B: 94.12% (73.12 to 98.95)*	A: 55.56% (32.15 to 76.73)* B: 40% (22.86 to 60)*	A: 5.08 (0.84 to 30.61)* B: 3.64 (0.62 to 21.38)*	A: 0.18 (0.07 to 0.49)* B: 0.34 (0.15 to 0.77)*	NR
Detection of Metastatic Disease									
Kumar, 2011[29] Poor	A: ^{68}Ga-DOTATOC PET/CT B: Contrast enhanced CT	Detection of metastatic disease, per-patient analysis	A: 92.8% (66 to 98.8) B: 57.1% (28.9 to 82.2)	A: 100% (54 to 100) B: 100% (54 to 100)	A: 100% (75.1 to 100) B: 100% (62.9 to 100)	A: 85.7% (42.2 to 97.6)* B: 50% (21.2 to 78.7)*	Unable to calculate	Unable to calculate	NR
Putzer, 2009[32] Fair	A: ^{68}Ga-DOTATOC PET B: CT	Detection of bone metastases, per-patient analysis	A: 97.37% (86.19 to 99.93)* B: 57.89% (40.82 to 73.69)*	A: 92.31% (63.97 to 99.81)* B: 100% (75.29 to 100)*	A: 97.37% (84.90 to 99.59)* B: 100%*	A: 92.31% (63.29 to 98.82)* B: 44.83% (35.88 to 54.12)*	A: 12.66 (1.92 to 83.27)* B: Unable to calculate	A: 0.03 (0.00 to 0.20)* B: 0.42 (0.29 to 0.61)*	NR
Schraml, 2013[34] Fair	A: ^{68}Ga-DOTATOC PET/CT B: MRI C: ^{68}Ga-DOTATOC PET D: CT	Detection of metastatic disease, per-patient analysis	A: 97.56% (87.14 to 99.94)* B: 97.56% (87.14 to 99.94)* C: 87.80% (73.80 to 95.92)* D: 90.24% (76.87 to 97.28)*	A: 100% (69.15 to 100)* B: 90% (55.50 to 99.75)* C: 90.00% (55.50 to 99.75)* D: 90.00% (55.50 to 99.75)*	A: 100%* B: 97.56% (86.16 to 99.61)* C: 97.30% (84.82 to 99.57)* D: 97.37% (85.18 to 99.58)*	A: 90.91% (59.06 to 98.58)* B: 90.00% (56.22 to 98.44)* C: 64.29% (43.56 to 80.76)* D: 69.23% (46.44 to 85.38)*	A: Unable to calculate B: 9.76 (1.52 to 62.67)* C: 8.78 (1.36 to 56.57)* D: 9.02 (1.40 to 58.09)*	A: 0.02 (0.00 to 0.17)* B: 0.03 (0.00 to 0.19)* C: 0.14 (0.06 to 0.32)* D: 0.11 (0.04 to 0.28)*	A: 98% (90 to 100) B: 96% (87 to 100) C: 88% (76 to 96) D: 90% (76 to 96

Table 4c. Studies of Diagnostic Accuracy of SSTR-PET for Identification of NETs

Author, Year Quality	Imaging Test	Analysis Method	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)	Imaging Accuracy
Schreiter, 2012[35] Fair	A: ^{68}Ga-DOTATOC PET/CT B: MRI C: CT D: ^{68}Ga-DOTATOC PET E: ^{68}Ga-DOTATOC PET-MRI	Differentiation of liver metastases from NET lesions, per-lesion analysis	A: 73.5% (64.3 to 81.3) B: 87.6% (80.1 to 93.1) C: 68.1% (58.7 to 76.6) D: 53.1% (43.5 to 62.5) E: 91.2% (84.3 to 95.7)	A: 88.2% (78.6 to 99.1) B: 86.8% (76.4 to 93.8) C: 85.3% (74.6 to 92.7) D: 79.4% (74.6 to 92.7) E: 95.6% (87.6 to 99.1)	A: 93.4% (87.4 to 97.1) B: 92.6% (86.5 to 96.6) C: 91.9% (85.6 to 96) D: 89.0% (85.6 to 96) E: 97.4% (92.6 to 99.5)	A: 69.4% (59.3 to 78.3) B: 82.9% (73 to 90.3) C: 65.4% (55.4 to 74.4) D: 56.2% (46.9 to 65.2) E: 87.2% (77.7 to 93.7)	Unable to calculate	Unable to calculate	NR
Detection of Unknown Primary or Metastatic NETs									
Sadowski, 2016[33] Poor	A: ^{68}Ga-DOTATATE PET/CT B: CT and/or MRI	Detection of GEP NETs, per-lesion analysis	A: 95.1% (92.4 to 96.8) B: 45.3% (37.9 to 52.9)	NR	Unable to calculate	Unable to calculate	Unable to calculate	Unable to calculate	NR

*Calculated

Abbreviations: CE= contrast enhanced; CI=confidence interval; CT= computed tomography; F= fluorine; FDG= fluorodeoxyglucose; Ga= gallium; GEP= gastroenteropancreatic; GEPNET= gastroenteropancreatic neuroendocrine tumors; HYNIC= hydrazinonicotinyl-Tyr3; In= indium; MBq; megabecquerel; MDCT= multidetector computed tomography; MRI= magnetic resonance imaging; NET= neuroendocrine tumor; NLR=negative liklihood ratio; NPV= negative predictive value; NR= not reported; PET= positron emission tomography; PLR=positive liklihood ratio; PPV= positive predictive value; SPECT= single photon emission computed tomography.

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Study Design	Population Characteristics	Eligibility Criteria	Number Approached, Eligible, Enrolled, Analyzed	Country & Setting	Duration of Follow-up	Attrition
Deppen, 2016[24]	Prospective cross-sectional	Age (mean, years): 53.7 (SD 11) Female: 58% NET type: -Midgut carcinoid: 45% -GEP: 23% -Unknown primary: 12% -Symptoms only: 7% -Pulmonary: 7% -Hindgut or rectal: 3% -Other: 2% Ki-67 category: -Low: 24 -Intermediate: 37 -High: 6 -Missing: 30	Enrolled patients having a proven diagnosis of NET, prospective analysis of safety and toxicity data and ^{68}Ga-DOTATATE scan findings. Patients were excluded if no prior ^{111}In-Pentetreotide was available, time between scans exceeded 3 years, no 111In-Pentetreotide scan available after a major surgical intervention occurring between the scans.	Approached: NR Eligible: NR Enrolled: 97 Analyzed: 78	USA Setting unclear	NR	NR
Frilling, 2010[45]	Prospective cohort	Age (mean, years): 52; range: 24-76 Female: 52% Primary tumor -Pancreas: 52% -Gastrointestinal tract: 37% -Biliary system: 6% -Lung: 5%	NR	Approached: NR Eligible: NR Enrolled: 52 Analyzed: 52	Germany Departments of Nuclear Medicine and Diagnostic and Interventional Radiology and Neuroradiology	NR	NR

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Confounders Adjusted for in Analysis	Imaging Tests	Outcomes	Adverse Events/Harms	Sponsor	Quality Rating
Deppen, 2016[24]	NR	^{68}Ga-DOTATATE PET/CT vs. ^{111}In-pentetreotide SPECT/CT	**Change in management:** 37%	No SAEs reported 3 minor AEs (minor itching the day after injection, unexplained drop in post scan oxygen saturation on room air [98% to 90%], and asymptomatic post scan tachycardia of 112 with a baseline heart rate of 87)	VA Merit Review I01BX007080, SNMMI Clinical Trials Network, Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS/NIH)	Poor
Frilling, 2010[45]	NR	^{68}Ga-DOTATATE PET/CT vs. CT vs. MRI	**Change in management:** 31/52 (60%), 14 patients had changes in surgical strategy and 17 patients had changes to non-surgical treatments	NR	The Dr. Heinz-Horst Deichmann Foundation	Poor

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Study Design	Population Characteristics	Eligibility Criteria	Number Approached, Eligible, Enrolled, Analyzed	Country & Setting	Duration of Follow-up	Attrition
Froeling, 2012[26]	Retrospective	Age (mean, years): 41.4; range: 16-78 Female: 48%	MEN syndrome verified hstopathologically or by clinical parameters and imagin modalities.	Approached: NR Eligible: NR Enrolled: 21 Analyzed: 21	Germany Setting unclear	Mean: 37.8 months	NR
Gabriel, 2007[27]	Prospective cohort	Age (mean, years): 58.2; range: 28-79 Female: 43% Enrolled for initial detection: 15% Enrolled for staging: 43% Enrolled for post therapy follow-up: 42%	Unclear	Approached: NR Eligible: NR Enrolled: 84 Analyzed: 84	Austria Department of Nuclear Medicine	NR	NR
Sadowski, 2015[44]	Prospective cohort	Age (mean, years): 42 (SD 15); range: 19-82 Female: 35%	NR	Approached: NR Eligible: NR Enrolled: 26 Analyzed: 26	USA NIH Clinical Center	NR	NR

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Confounders Adjusted for in Analysis	Imaging Tests	Outcomes	Adverse Events/Harms	Sponsor	Quality Rating
Froeling, 2012[26]	NR	^{68}Ga-DOTATOC PET/CT vs. ^{68}Ga-DOTATOC PET vs. CT	**Change in treatment:** 47.6% (10/21); 9 patients had an additional indication for surgery and 1 had an additional surgery and a cancellation of a surgery; no change in pharmacotherapy.	NR	NR	Poor
Gabriel, 2007[27]	NR	^{68}Ga-DOTATOC PET vs. ^{99m}Tc-HYNIC-TOC or ^{111}In-DOTATOC SPECT/CT or CT	**Clinically valuable information** Vs. CT alone: 21.4% (18/84) Vs. SPECT: 14.3% (12/84)	No side effects were noted after tracer injection	NR	Poor
Sadowski, 2015[44]	NR	^{68}Ga-DOTATATE PET/CT vs. ^{111}In-pentetreotide SPECT/CT vs.CT vs. MRI	**Change in management:** 8/26 (31%), 7 patients had surgical resection of the primary or metastatic disease and 1 patient had systemic therapy recommended for progressive metastatic NETs.	NR	Center for Cancer Research, National Cancer Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health	Poor

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Study Design	Population Characteristics	Eligibility Criteria	Number Approached, Eligible, Enrolled, Analyzed	Country & Setting	Duration of Follow-up	Attrition
Sadowski, 2016[33]	Prospective cross-sectional	Age (mean, years): 51; range: 19-82 Female: 56% Patients with symptoms: 55% Chromogranin A (median, ng/mL): 87.5; range: 20-18,710 Previous surgery: 77.5% -Pancreatic NET: 44.9% -Gastro-enteric NET: 55.1% Prior proven NET -Pancreatic: 27.5% -Small/large bowel: 23.7%/3.0% -Insulinoma: 5.3% -Gastric: 5.3% -Thymic carcinoid: 0.8% -Vipoma: 1.5% -Lung: 0.8%	Nonpregnant patients ≥18 years old, suspected or known to have GEPNETs on imaging (CT, MRI, ^{18}F-FDG PET) and/or biochemical evidence of GEPNETs, and/or a familial predisposition to NET (MEN1 or von Hippel-Lindau).	Approached: NR Eligible: NR Enrolled: 131 Analyzed: 131	USA Setting unclear	NR	NR

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Confounders Adjusted for in Analysis	Imaging Tests	Outcomes	Adverse Events/Harms	Sponsor	Quality Rating
Sadowski, 2016[33]	NR	^{68}Ga-DOTATATE PET/CT vs. ^{111}In-pentetreotide SPECT/CT vs. CT vs. MRI	**Change in management:** 32.8% (43/131)	NR	Intramural Research Programs of the Center for Cancer Research, National Cancer Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases at the NIH	Poor

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Study Design	Population Characteristics	Eligibility Criteria	Number Approached, Eligible, Enrolled, Analyzed	Country & Setting	Duration of Follow-up	Attrition
Van Binnebeek, 2016[36]	Prospective trial	Age (mean, years): 59; range: 31-80 Female: 57% Primary site -GEP: 74% -Lung: 7.5% -Merckel cell carcinomas: 3.9% -Breast: 1.8% -Kidney: 1.8% -Other/unknown: 11%	Patients with metastatic NET, enrolled in a prospective phase II monocentric trial.	Approached: NR Eligible: NR Enrolled: 53 Analyzed: 53	Belgium University hospital	NR	NR

Table 4d. Studies of Treatment Changes due to SSTR-PET for Identification of NETs

Author, Year	Confounders Adjusted for in Analysis	Imaging Tests	Outcomes	Adverse Events/Harms	Sponsor	Quality Rating
Van Binnebeek, 2016[36]	NR	^{68}Ga-DOTATOC PET/CT vs. ^{111}In-pentetreotide SPECT/CT	**Change in management:** 13% (7/53)	NR	NR	Poor

Abbreviations: AE= adverse effect; CT= computed tomography; F= fluorine; FDG= fluorodeoxyglucose; Ga= Gallium; GEPNET= gastroenteropancreatic neuroendocrine tumor; HYNIC-octreotide= hydrazinonicotinyl-Tyr3-octreotide; In= indium; MEN1= multiple endocrine neoplasia type 1; MRI= magnetic resonance imaging; NET= neuroendocrine tumor; NIH= National Institutes of Health; NR= not reported; PET= positron emission tomography; SAE= serious adverse effects; SD= standard deviation;SNMMI= Society of Nuclear Medicine and Molecular Imaging; SPECT= single photon emission computed tomography.

Appendix 5. Quality Assessment Criteria

Cohort Studies

Initial Assembly of Comparable Groups

- Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort)?
- Were the groups comparable at baseline?
- Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?

Maintenance of Comparable Groups

- Did the article report attrition?
- Is there important differential loss to follow-up or overall high loss to follow-up?

Measurements: Equal, Reliable, and Valid

- Were outcomes pre-specified and defined, and ascertained using accurate methods?
- Were outcome assessors and/or data analysts blinded to treatment?
- Did the study perform appropriate statistical analyses on potential confounders?

Response options for all questions: Yes, no, unclear, or not applicable

Overall rating options: Good, fair, or poor

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual[18]

Appendix 5. Quality Assessment Criteria

Diagnostic Accuracy Studies

Patient Selection

- Was a consecutive or random sample of patients enrolled?
- Was a case-control design avoided?
- Did the study avoid inappropriate exclusions?

Index Test(s)

- Were the index test results interpreted without knowledge of the results of the reference standard?
- If a threshold was used, was it pre-specified?

Reference Standard

- Is the reference standard likely to correctly classify the target condition?
- Were the reference standard results interpreted without knowledge of the results of the index text?

Flow and Timing

- Was there an appropriate interval between index test(s) and reference standard?
- Did all patients receive a reference standard?
- Did patients receive the same reference standard?
- Were all patients included in the analysis?

Response options for all questions: Yes, no, unclear, or not applicable

Overall rating options: Good, fair, or poor

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (>100) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients (i.e. applicable to most screening settings).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Source: Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) Criteria[19]

Appendix 6. Quality Assessment Tables

Table 6a. Quality Assessment of Studies of Diagnostic Accuracy

	Patient Selection			Index Test(s)		Reference Standard	
Author, year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted with out knowledge of the results of the index text?
Deppen, 2016[24]	Yes, consecutive	No	Yes	Yes	Not applicable	Yes	Unclear
Etchebehere, 2014[25]	Yes, consecutive	No	Yes	Yes	Not applicable	Unclear	No
Froeling, 2012[26]	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Gabriel, 2007[27]	Yes, consecutive	Yes	Yes	Yes	Not applicable	Yes	Yes
Has Simsek, 2014[28]	Yes, consecutive	No	Yes	Unclear	Not applicable	Unclear	Yes
Kumar, 2011[29]	Unclear	Unclear	Unclear	Yes	Not applicable	Yes	No
Lococo, 2015[30]	Yes, consecutive	No	Yes	Yes	Not applicable	Yes	Unclear
Morgat, 2016[31]	Yes, consecutive	No	Yes	Yes	Not applicable	Yes	No
Putzer, 2009[32]	Unclear	No	Unclear	Yes	Not applicable	Yes	No
Sadowski, 2016[33]	Unclear	Yes	Unclear	Yes	Not applicable	Yes	Unclear
Schraml, 2013[34]	Yes, consecutive	No	Unclear	Yes	Not applicable	Yes	No
Schreiter, 2012[35]	Yes, consecutive	No	Yes	Unclear	Yes	Yes	Unclear
Van Binnebeek, 2016[36]	Unclear	No	Unclear	Yes	Not applicable	Unclear	No
Venkitaraman, 2014[37]	Yes, all	Yes	Yes	Yes	Not applicable	Yes	Yes
Versari, 2010[38]	Yes, consecutive	Yes	Yes	No	Not applicable	Yes	No

Table 6a. Quality Assessment of Studies of Diagnostic Accuracy

	Flow and Timing				
Author, year	**Was there an appropriate interval between index test(s) and reference standard?**	**Did all patients receive a reference standard?**	**Did patients receive the same reference standard?**	**Were all patents included in the analysis?**	**Quality rating**
Deppen, 2016[24]	Yes	No	No	Yes	Fair
Etchebehere, 2014[25]	Yes	Yes	No	Yes	Fair
Froeling, 2012[26]	Yes	Yes	Yes	Yes	Fair
Gabriel, 2007[27]	Yes	Yes	Yes	Yes	Good
Has Simsek, 2014[28]	Yes	Yes	Yes	Yes	Poor
Kumar, 2011[29]	Unclear	Yes	Yes	Yes	Poor
Lococo, 2015[30]	Yes	Yes	Yes	Yes	Poor
Morgat, 2016[31]	Yes	Yes	Yes	Yes	Fair
Putzer, 2009[32]	Yes	Yes	Yes	Yes	Fair
Sadowski, 2016[33]	Unclear	Yes	Unclear	Yes	Poor
Schraml, 2013[34]	Yes	Yes	Unclear	Yes	Fair
Schreiter, 2012[35]	Unclear	Yes	Yes	Yes	Fair
Van Binnebeek, 2016[36]	Yes	Yes	No	Yes	Poor
Venkitaraman, 2014[37]	Unclear	Yes	Yes	Yes	Good
Versari, 2010[38]	Yes	Yes	No	Yes	Fair

Table 6b. Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort)?	Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report attrition?	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating
Deppen, 2016[24]	Yes, consecutive	Yes	Yes	No	Unclear	No	Poor
Frilling, 2010[45]	Yes, consecutive	Yes	No	No	Unclear	No	Poor
Froeling, 2012[26]	Unclear	Yes	Yes	No	Unclear	No	Poor
Gabriel, 2007[27]	Yes, consecutive	Yes	Yes	No	Unclear	No	Poor
Sadowski, 2015[44]	Unclear	Yes	No	No	Unclear	No	Poor
Sadowski, 2016[33]	Unclear	Yes	Yes	No	Unclear	No	Poor
Van Binnebeek, 2016[36]	Unclear	Yes	Yes	No	Unclear	No	Poor

Appendix 7. Strength of Evidence Table

Outcome	Number of Studies Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Strength of Evidence	Main Findings
Key Question 1. Diagnostic accuracy of SSTR-PET versus OctreoScan, FDG-PET, or CT/MRI							
SSTR-PET vs. Octreoscan							
NETs*							
Sensitivity	5 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	• 97% vs. 83%, p=0.01 • 96% vs. 60%, p=0.03
Specificity	2 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	• No differences
GEP NETs							
Sensitivity	1 diagnostic accuracy study	Moderate	Unable to assess	No indirectness	Imprecise	Very low	• 76% vs. 20%, p<0.0001
Specificity	1 diagnostic accuracy study	Moderate	Unable to assess	No indirectness	Imprecise	Very low	• 100% vs. 50%, p<0.01
Metastatic NETs							
Sensitivity	2 diagnostic accuracy studies	High	No inconsistency	No indirectness	No imprecision	Low	• 95% vs. 31%, p<0.001 • 99.9% vs. 60%, p<0.01
Specificity	No studies	--	--	--	--	--	• No data
SSTR-PET vs. FDG-PET							
GEP NETs							
Sensitivity	2 diagnostic accuracy studies	High	No inconsistency	No indirectness	Imprecise	Very low	• 95% vs. 37%, p not reported • 100% vs. 25%, p=0.03
Specificity	No studies	--	--	--	--	--	• No data
Pulmonary carcinoid							
Sensitivity	2 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	• 96% (80% to 99.9%)vs. 69% (48% to 86%) • 79% vs. 55%, p=0.13
Specificity	1 diagnostic accuracy study	Low	Unable to assess	No indirectness	Imprecise	Low	• No differences
SSTR-PET vs. CT/MRI							
NETs*							
Sensitivity	2 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	• 97% vs. 61%, p<0.001 • 96% vs. 72%, p=0.08
Specificity	2 diagnostic accuracy studies	Moderate	Inconsistent	No indirectness	Imprecise	Very low	• 92% vs. 71%, p<0.001 • 97% vs. 100%
GEP NETs							
Sensitivity	4 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	• 76% vs. 60%, p<0.0001 • 92% vs. 43%, p<0.001 • 85% vs. 73%, p>0.05 • 100% vs. 83%, p=0.06
Specificity	3 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	• 100% vs. 50%, p<0.01 • 94% vs. 61%, p<0.001 • 83% vs. 80%, p>0.05

Appendix 7. Strength of Evidence Table

Outcome	Number of Studies Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Strength of Evidence	Main Findings
Unknown primary or metastatic NET							
Sensitivity	1 diagnostic accuracy study	High	Unable to assess	No indirectness	Imprecise	Very low	• 95% vs. 45%, p<0.001
Specificity	No studies	--	--	--	--	--	• No data
Metastatic NETs							
Sensitivity	3 diagnostic accuracy studies	Moderate	Inconsistent	No indirectness	Imprecise	Very low	• 97% vs. 58%, p<0.001 • 90% to 98% across modalities • 74% vs. 68% to 88%
Specificity	3 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	• 92% vs. 99.8% • 90% to 100% across modalities • 85% to 88% across modalities
Key Question 2. Predictive utility of SSTR-PET for predicting response to somatostatin analogue therapy or PRRT or somatostatin analogue therapy							
Diagnostic accuracy	No comparative studies	--	--	--	--	--	• No comparative studies; 2 studies of SSTR-PET/CT reported sensitivity/specificity of 75% and 64% for response to octreotide (well-differentiated NET of ileum) and sensitivity/specificity of 95% and 60% for response to PRRT (metastatic NET)
Key Question 3. Effects of SSTR-PET for restaging on quality of life, patient management†, and patient clinical outcomes							
Proportion of patients with treatment change	6 uncontrolled studies	High	No inconsistency	No indirectness	No imprecision	Very low	• Proportion with change in management ranged from 8.4% to 60%, most studies reported >30%

Abbreviations: CT= computed tomography; FDG= fluorodeoxyglucose; GEP= gastroenteropancreatic; MRI= magnetic resonance imaging; NET= neuroendocrine tumor; PET= positron emission tomography; PRRT= peptide receptor radionuclide therapy; SSTR= somatostatin receptor.