

Evidence Synthesis - Rapid Review

Systematic Review: Somatostatin Imaging for Neuroendocrine Tumors

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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 (Tyr³)-octreotate) positron emission tomography (PET) versus functional imaging with octreotide coupled with radiolabeled indium-111 and the chelator diethylenetriaminepentaacetic 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 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 ¹⁸FDG-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 ¹⁸F¹⁸FDG-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 SSSTR-PET for predicting response to somatostatin therapy or PRRT and effects on clinical-decision-making.

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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 (¹¹¹In-DTPA, also referred to as ¹¹¹In-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 (Tyr³)-octreotate (TATE) and edotreotide (TOC), coupled with positron emitting isotopes such as gallium-68 (⁶⁸Ga) 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 ⁶⁸Ga-DOTATATE and ⁶⁸Ga-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 ⁶⁸Ga-DOTATATE or ⁶⁸Ga-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}F 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, ¹⁸FDG-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, ¹⁸FDG-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, ¹⁸FDG-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 criteria¹⁸ for randomized trials and cohort studies, and QUADAS-2¹⁹ (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, ¹⁸FDG-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 ¹⁸FDG-PET, and ten studies compared SSTR-PET with CT or MRI. Four studies used ⁶⁸Ga-DOTATATE and ten used ⁶⁸Ga-DOTATOC; one study used ⁶⁸Ga-DOTATATE, ⁶⁸Ga-DOTATOC, or ⁶⁸Ga-DOTANOC.³⁰ Four studies evaluated accuracy for detection of various NETs (primarily gastroenteropancreatic³⁹ 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 ⁶⁸Ga-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

⁶⁸Ga-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 ($\geq 95\%$) 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 ⁶⁸Ga-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 ⁶⁸Ga-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 ⁶⁸Ga-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 ¹⁸FDG-PET

Four studies ($n=20$ to 32) compared the diagnostic accuracy of SSTR-PET/CT with ¹⁸FDG-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 ¹⁸FDG-PET.

For diagnosis of GEP NETs, one poor-quality study ($n=27$) found ⁶⁸Ga-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 ⁶⁸Ga-DOTATOC PET/CT (n=20) associated with higher sensitivity than ¹⁸FDG-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 ¹⁸FDG PET/CT using a per-patient analysis.^{30,37} One good-quality study (n=32) found ⁶⁸Ga-DOTATOC PET/CT associated with higher sensitivity than ¹⁸FDG 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 ⁶⁸Ga-DOTATOC, ⁶⁸Ga-DOTATATE, or ⁶⁸Ga-DOTANOC PET/CT associated with higher sensitivity than ¹⁸FDG-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 ¹⁸FDG 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}F 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}F FDG PET/CT for all tumor grades, though the difference in sensitivity between SSTR-PET/CT and ^{18}F 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 study²⁴ 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}F 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, ¹⁸FDG-PET, and/or CT/MRI for predicting response to PRRT or somatostatin analogue therapy?

No study compared the utility of SSTR-PET versus OctreoScan, ¹⁸FDG-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, ¹⁸FDG-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 Belgium³⁶ 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}F 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}F FDG-PET/CT²⁸ and one study found SSTR-PET more accurate than ^{18}F 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 (⁶⁸Ga-DOTATATE and ⁶⁸Ga-DOTATOC) and octreotide SPECT/CT (¹¹¹In-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.

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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 Imaging 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:

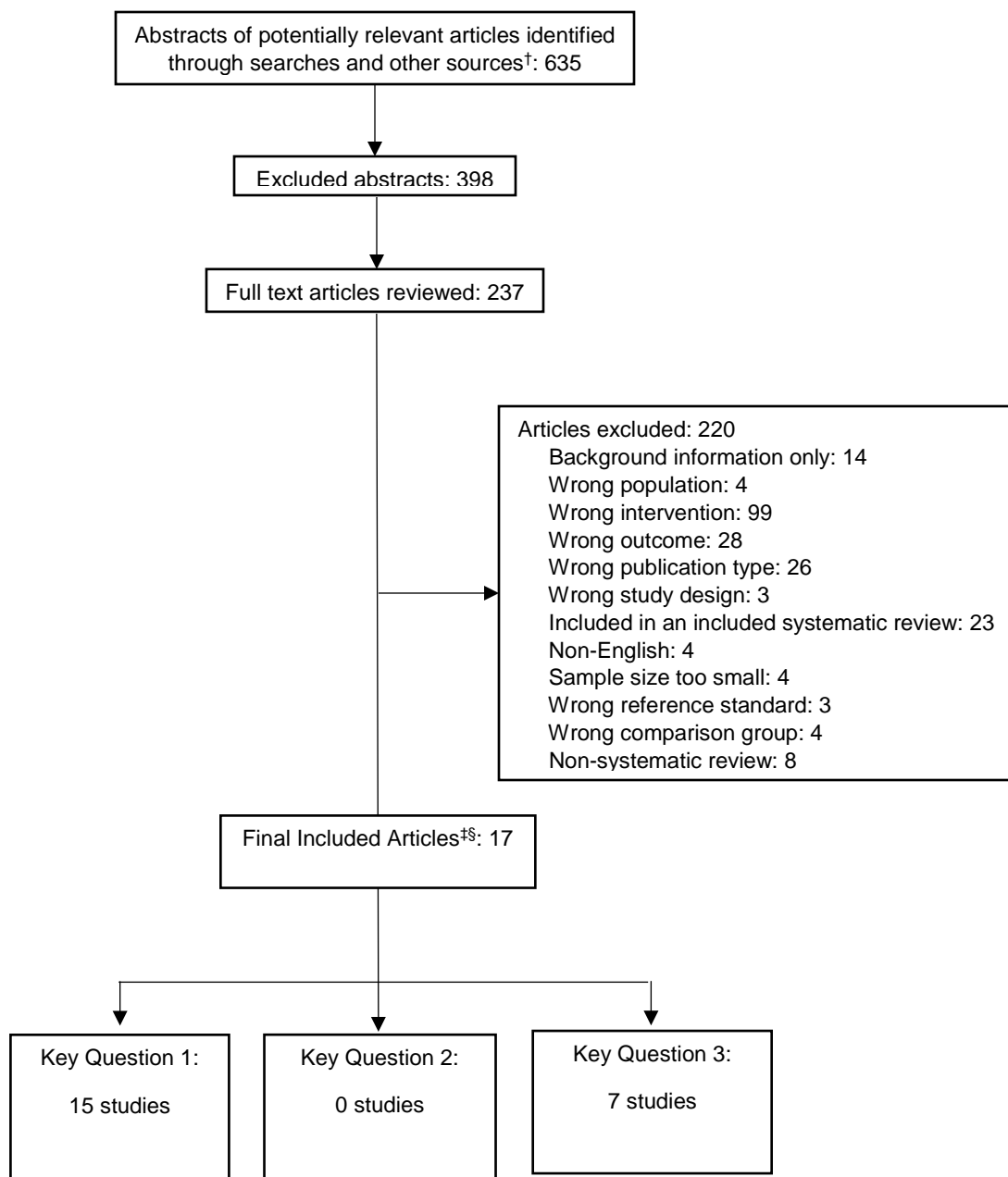
-
- 1 exp Somatostatin/ (536)
 - 2 Receptors, Somatostatin/ (32)
 - 3 (somatostatin receptors or SSTR).mp. (59)
 - 4 Positron-Emission Tomography/ (789)
 - 5 PET.ti,ab. (2435)
 - 6 exp Tomography, X-Ray Computed/ (3949)
 - 7 (DOTATOC or DOTATATE).mp. [mp=title, original title, abstract, mesh headings, 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 ¹¹¹ In-Pentetreotide scan available after a major surgical intervention occurring 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 comparison 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 comparison 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	Analyzed 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 from adjacent 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 visual 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 imaging 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
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 evidence 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 evidence 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	Uncl ear	Uncl ear	92.8% (66 to 98.8)
Kumar, 2011 ²⁹ Poor	Same as above	Same as above	N=8 100%	Detection of metastatic disease	2	Unc lear	Uncl ear	Uncl ear	20% (3.1 to 55.5)
Kumar, 2011 ²⁹ Poor	Same as above	Same as above	N=20 100%	Detection of metastatic disease	7	Unc lear	Uncl ear	Uncl ear	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 Association 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
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
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, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant 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 characteristics.	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 system: 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, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant 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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET/CT	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant 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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET/CT	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant 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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET/CT	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant 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 characteristics.	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, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant 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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET/CT	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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 characteristics.	Same as above	Same as above	Same as above
Schraml, 2013 ³⁴ Fair	⁶⁸ Ga-DOTATOC	PET	In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant 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 characteristics.	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.	Maintenance 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 likelihood ratio; NPV=negative predictive value; NR= not reported; PET= positron emission tomography; PLR=positive likelihood 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 ^{99m} Tc-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 comparison to the adjacent tissues was seen in the coronal, transaxial, and sagittal views. B: Intense focal uptake in comparison to the adjacent tissues was seen in the coronal, transaxial, and sagittal views. C: Analyzed 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 Association 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, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. This was combined with the CT assessment using standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics. B: Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics. C: In PET images, focal uptake exceeding normal regional tracer accumulation was classified as a malignant lesion. D: Based on standard reading criteria established in clinical practice by taking into account morphologic features and enhancement characteristics.	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.	Maintenance 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									
<i>Detection of NETs</i>									
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 ^{99m} Tc-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%
<i>Detection of GEP NETs</i>									
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
<i>Detection of Unknown Primary or Metastatic NETs</i>									
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
<i>Detection of metastatic disease</i>									
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. ¹⁸FDG-PET									
<i>Detection of GEP NETs</i>									
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
<i>Detection of Pulmonary Carcinoids</i>									
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%
<i>Detection of Metastatic Disease</i>									
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									
<i>Detection of NETs</i>									
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%
<i>Detection of GEP NETs</i>									
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
<i>Detection of Metastatic Disease</i>									
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
<i>Detection of Unknown Primary or Metastatic NETs</i>									
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 likelihood ratio; NPV= negative predictive value; NR= not reported; PET= positron emission tomography; PLR=positive likelihood ratio; PPV= positive predictive value; SPECT= single photon emission computed tomography.

Table 4d. Studies of Treatment Changes due to SSSTR-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 ¹¹¹ In-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 histopathologically 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	<p>Age (mean, years): 51; range: 19-82</p> <p>Female: 56%</p> <p>Patients with symptoms: 55%</p> <p>Chromogranin A (median, ng/mL): 87.5; range: 20-18,710</p> <p>Previous surgery: 77.5%</p> <p>-Pancreatic NET: 44.9%</p> <p>-Gastro-enteric NET: 55.1%</p> <p>Prior proven NET</p> <p>-Pancreatic: 27.5%</p> <p>-Small/large bowel: 23.7%/3.0%</p> <p>-Insulinoma: 5.3%</p> <p>-Gastric: 5.3%</p> <p>-Thymic carcinoid: 0.8%</p> <p>-Vipoma: 1.5%</p> <p>-Lung: 0.8%</p>	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).	<p>Approached: NR</p> <p>Eligible: NR</p> <p>Enrolled: 131</p> <p>Analyzed: 131</p>	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 $\geq 80\%$); 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 Manual¹⁸

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 test?

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) Criteria¹⁹

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*							
<i>Sensitivity</i>	5 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> 97% vs. 83%, p=0.01 96% vs. 60%, p=0.03
<i>Specificity</i>	2 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> No differences
GEP NETs							
<i>Sensitivity</i>	1 diagnostic accuracy study	Moderate	Unable to assess	No indirectness	Imprecise	Very low	<ul style="list-style-type: none"> 76% vs. 20%, p<0.0001
<i>Specificity</i>	1 diagnostic accuracy study	Moderate	Unable to assess	No indirectness	Imprecise	Very low	<ul style="list-style-type: none"> 100% vs. 50%, p<0.01
Metastatic NETs							
<i>Sensitivity</i>	2 diagnostic accuracy studies	High	No inconsistency	No indirectness	No imprecision	Low	<ul style="list-style-type: none"> 95% vs. 31%, p<0.001 99.9% vs. 60%, p<0.01
<i>Specificity</i>	No studies	--	--	--	--	--	<ul style="list-style-type: none"> No data
SSTR-PET vs. FDG-PET							
GEP NETs							
<i>Sensitivity</i>	2 diagnostic accuracy studies	High	No inconsistency	No indirectness	Imprecise	Very low	<ul style="list-style-type: none"> 95% vs. 37%, p not reported 100% vs. 25%, p=0.03
<i>Specificity</i>	No studies	--	--	--	--	--	<ul style="list-style-type: none"> No data
Pulmonary carcinoid							
<i>Sensitivity</i>	2 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> 96% (80% to 99.9%) vs. 69% (48% to 86%) 79% vs. 55%, p=0.13
<i>Specificity</i>	1 diagnostic accuracy study	Low	Unable to assess	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> No differences
SSTR-PET vs. CT/MRI							
NETs*							
<i>Sensitivity</i>	2 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> 97% vs. 61%, p<0.001 96% vs. 72%, p=0.08
<i>Specificity</i>	2 diagnostic accuracy studies	Moderate	Inconsistent	No indirectness	Imprecise	Very low	<ul style="list-style-type: none"> 92% vs. 71%, p<0.001 97% vs. 100%
GEP NETs							
<i>Sensitivity</i>	4 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> 76% vs. 60%, p<0.0001 92% vs. 43%, p<0.001 85% vs. 73%, p>0.05 100% vs. 83%, p=0.06
<i>Specificity</i>	3 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> 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							
<i>Sensitivity</i>	1 diagnostic accuracy study	High	Unable to assess	No indirectness	Imprecise	Very low	<ul style="list-style-type: none"> 95% vs. 45%, p<0.001
<i>Specificity</i>	No studies	--	--	--	--	--	<ul style="list-style-type: none"> No data
Metastatic NETs							
<i>Sensitivity</i>	3 diagnostic accuracy studies	Moderate	Inconsistent	No indirectness	Imprecise	Very low	<ul style="list-style-type: none"> 97% vs. 58%, p<0.001 90% to 98% across modalities 74% vs. 68% to 88%
<i>Specificity</i>	3 diagnostic accuracy studies	Moderate	No inconsistency	No indirectness	Imprecise	Low	<ul style="list-style-type: none"> 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							
<i>Diagnostic accuracy</i>	No comparative studies	--	--	--	--	--	<ul style="list-style-type: none"> 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							
<i>Proportion of patients with treatment change</i>	6 uncontrolled studies	High	No inconsistency	No indirectness	No imprecision	Very low	<ul style="list-style-type: none"> 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.