^{68}Ga-DOTATATE compared to ^{111}In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis

Stephen A. Deppen PhD[1,2,7], Jeffrey Blume PhD[3], Adam J. Bobbey MD[4], Chirayu Shah MD,[1,6] Michael M Graham PhD, MD[5], Patricia Lee MLS[6], Dominique Delbeke, MD, PhD[6,7], Ronald C Walker, MD[1,4,6,7]

Affiliations:

[1]Veterans Affairs Hospital, VA Tennessee Valley Healthcare System, Nashville TN

[2]Department of Thoracic Surgery, Vanderbilt University Medical Center, Nashville TN

[3]Department of Biostatistics, Vanderbilt University, Nashville TN

[4]Department of Radiology, Nationwide Children's Hospital, Columbus, OH

[5]Department of Radiology, University of Iowa, Iowa City, IA

[6]Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville TN

[7]Vanderbilt-Ingram Cancer Center, Nashville, TN

Corresponding Author/Request for Reprints:

Ronald C. Walker, MD, FACNM, FACR
Department of Radiology & Radiological Sciences
Vanderbilt University Medical Center
1121 21st Avenue South CCC-1121 MCN
Nashville, TN 37232-2675
ronald.walker@vanderbilt.edu

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ABSTRACT

Purpose Neuroendocrine tumors (NETs) are uncommon tumors with increasing incidence and prevalence. Current reports suggest ^{68}Ga-DOTATATE PET/CT imaging improves diagnosis and staging of NETs compared to ^{111}In-DTPA-octreotide (**octreotide**) and conventional imaging. We performed a systematic review of ^{68}Ga-DOTATATE for safety and efficacy compared to octreotide and conventional imaging to determine if available evidence supports US FDA approval.

Methods Medline, EMBASE, Web of Science and Cochrane Reviews electronic databases were searched from January 1999, through September 2015. Results were restricted to human studies comparing diagnostic accuracy of ^{68}Ga-DOTATATE to octreotide or conventional imaging for pulmonary or gastroenteropancreatic (**GEP**) NET, and for human studies reporting safety/toxicity for ^{68}Ga-DOTATATE with ≥10 subjects thought to have NETs. Direct communication with corresponding authors was attempted to obtain missing information. Abstracts meeting eligibility criteria were collected by a research librarian and assembled for reviewers; 2 reviewers independently determined whether or not to include each abstract. If either reviewer chose inclusion, the abstract was accepted for review.

Results Database and bibliography searches yielded 2479 articles, of which 42 were eligible. Three studies compared the two radiopharmaceuticals in the same patient, finding ^{68}Ga-DOTATATE to be more sensitive than octreotide. Nine studies compared ^{68}Ga-DOTATATE to conventional imaging. ^{68}Ga-DOTATATE estimated sensitivity, 90.9% (95%CI: 81.4%, 96.4%), and specificity, 90.6% (95%CI: 77.8%, 96.1%), were high. Five studies were retained for safety reporting only. Report of harm possibly

related to ^{68}Ga-DOTATATE was rare (6 of 974), and no study reported major toxicity or safety issues.

Conclusion No direct comparison of octreotide and ^{68}Ga-DOTATATE imaging for diagnosis and staging in an unbiased population of NETs has been published. Available information in the peer-reviewed literature regarding diagnostic efficacy and safety supports the use of ^{68}Ga-DOTATATE for imaging of NETs where it is available.

INTRODUCTION

Neuroendocrine tumors (NETs) are uncommon, with annual incidence approximately 50

per million persons, an almost five-fold increase since 1973. This increase in incidence

may partially reflect improvements in diagnosis. Estimated prevalence is 350 per

million[1, 2]. Conventional imaging (CI) approved in the United States for diagnosis,

staging, restaging, and assessment of treatment includes radiographs, computed

tomography (CT), magnetic resonance imaging (MRI), ultrasound (including endoscopic

ultrasound), skeletal scintigraphy, and somatostatin receptor scintigraphy (SSRS),

which is very useful for imaging NETs which typically express high levels of

somatostatin receptors[3].

^{111}In-DTPA-pentetreotide (octreotide) imaging, utilizing planar, SPECT or

SPECT/CT imaging at 4, 24, and sometimes 48 hours after injection, is the currently

approved SSRS imaging modality in the US. A breakthrough at the time,[4] octreotide

imaging limitations include relatively slow pharmacokinetics, high energy gamma

emissions and unfavorable patient dosimetry limiting injectable activity to about 37 – 74

MBq (1 - 2 mCi), all resulting in relatively low resolution images. Accordingly, newer,

higher-affinity somatostatin analogs, labeled with radioisotopes with more favorable

resolution and dosimetry, such as ^{68}Ga, a positron emitter, are promising SSRS

imaging agents.

While several ^{68}Ga-labeled SSRS imaging probes are reported,[5] this

systematic review and meta-analysis is limited to ^{68}Ga-labeled 4,7,10-tricarboxymethyl-

1,4,7,10-tetraaza-cyclododecan-1-yl-acetyl-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH

(^{68}Ga-DOTATATE) used in conjunction with positron emission tomography with integral

computed tomography (PET/CT). If ^{68}Ga-DOTATATE is equivalent to or better than octreotide imaging in safety and diagnostic efficacy, these results could support US FDA approval, hopefully contributing to routine use of ^{68}Ga-DOTATATE as the standard for SSRS imaging for patients with tumors with high expression of somatostatin receptor.

Several recent reviews describe ^{68}Ga-DOTATATE imaging of pulmonary or GEP neuroendocrine tumors(*5-9*), but do not limit their reviews to comparing ^{68}Ga-DOTATATE with octreotide imaging, combining results with other ^{68}Ga-labeled synthetic somatostatin analogs. The lack of direct comparison of ^{68}Ga-DOTATATE with octreotide imaging limits assessment of differential efficacy between these two radiopharmaceuticals. Previous reviews also did not summarize details of radiopharmaceutical compounding or observed ^{68}Ga-DOTATATE toxicity. This review assesses the efficacy of ^{68}Ga-DOTATATE compared to octreotide and CI, and reports compounding details and safety information with the range of reported harms observed with ^{68}Ga-DOTATATE, to determine if sufficient data are present to support ^{68}Ga-DOTATATE regulatory approval.

METHODS

This report follows PRISMA guidelines (http://www.prisma-statement.org/) systematic reviews and meta-analyses(*10*). Study selection and definition of objectives with clinical relevance follows the Population, Intervention, Comparison, Outcome, and Study Type (PICOS) method (Supplemental File 1).

Inclusion criteria are detailed in the PICOS table and include primary trials or studies with > 10 human subjects conducted to investigate diagnosis for pulmonary or

GEP NETs. Studies excluded were: 1) systematic reviews, meta-analyses or case reviews with n ≤ 10 subjects, 2) studies not reporting ^{68}Ga-DOTATATE compared to octreotide and/or CI, 3) studies without pulmonary or GEP NET histology, 4) studies reporting treatment, not diagnosis and 5) other reasons determined by reviewers making a study inapplicable. In studies with incomplete information, direct communication with the corresponding author was sought and, when provided, included in the analysis if the additional information allowed inclusion. Studies with overlapping populations were limited to the single report with the largest number of patients, or using the most recent imaging technology, as reported by the corresponding or senior author. Analysis was on a "per-patient" basis (i.e. diagnosis, staging and/or impact on management) since, in patients with multiple lesions (primary tumor and metastases), each of multiple lesions cannot be independently verified. Endpoint of cancer or benign diagnosis was established and included in data extraction. Gold standard definition, whether by pathology, imaging, or combination, was abstracted.

Study selection was from searching Medline, EMBASE, Cochrane Reviews electronic databases and grey literature from January, 1999 through September 29, 2015. There was no language restriction if an English translation for non-English articles or abstracts was available. Bibliographies from meta-analyses and literature reviews were examined separately, with papers of interest included in the final reviewed abstract list (Fig. 1, Flow diagram of studies from systematic review). Article search criteria included all discovered expressions of pulmonary or GEP neuroendocrine tumors. Separately, any of the common expressions of DOTATATE or Octreotide or

Pentetreotide or somatostatin or somatostatin-derived receptor were included. Formal search criteria and preliminary results for the Medline search are in Supplemental File 2.

Summary sensitivity, specificity and accuracy with 95%CIs were calculated for each imaging method, by study, when possible, though some studies only reported subjects with proven NET, precluding specificity measurements. Changes in treatments were abstracted from manuscripts. A random effects model of combined sensitivity and specificity was estimated. Study characteristics possibly influencing estimates of sensitivity and specificity were included as fixed effects. A hierarchical summary receiver operator curve (SROC) was not estimated because of too few studies.

Abstracts collected by a research librarian were reviewed independently by two clinician reviewers blinded to the other reviewer. If either reviewer determined that full data extraction was indicated, complete text review occurred with data extraction conducted independently by the reviewers. Conflicts were resolved by a third reviewer if needed. Any discrepancies in abstraction coding were resolved by consensus. Inter-rater reliability for study inclusion was measured by Cohen's kappa.

Quality Assessment

Reviewers assessed study quality according to prospective criteria using a modified Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) set of 13 questions (Supplement File 3)(*11, 12*). Questions addressed technical quality of index and reference tests, independence and accuracy of test interpretation, and sample size and population representation. Additional quality questions measured possible misclassification bias from preselection bias, incomplete diagnosis, or diagnosis driven

by scan results. A quality score (maximum possible 13) was created by adding the number of QUADAS criteria with which the study complied.

Harms were classified according to National Cancer Institute Common Toxicity Criteria for both metrics and grading of possible harms([13]). When related safety or outcomes for ^{68}Ga-DOTATATE were not reported, authors were contacted directly and requested to provide this information. All safety data are reported separately in Supplemental File 4. Other factors of interest abstracted from the study or via correspondence included: range of DOTATATE peptide mass, range of injected activity, number of patients receiving ^{68}Ga-DOTATATE, and whether the patients were receiving short- or long-acting octreotide medication at the time of ^{68}Ga-DOTATATE scanning.

RESULTS

The electronic search returned 2,476 articles; bibliography reviews added 3 more. Thus, 2,479 abstracts were screened. After initial review, 2,437 articles were excluded. Inclusion agreement between reviewers was 99%; Cohen's kappa was moderately high at 0.70. Article exclusion occurred for multiple reasons, most commonly the radiopharmaceutical was not ^{68}Ga-DOTATATE (N=795), the article described treatment and not diagnosis (N=578), or the article was a case review with ≤10 subjects (N=674) (Fig. 1). Forty-two studies received full review, with 25 excluded upon closer analysis. The remaining 17 met all inclusion criteria (Table 1). These 17 studies included 971 participants (Median 44; IRQ: 22, 51), average age 56 (95%CI: 56, 66), with 3 reporting direct comparison of ^{68}Ga-DOTATATE to octreotide and CI,([14-16]) 9 studies comparing ^{68}Ga-DOTATATE to CI,([17-25]) and 5 studies reporting comparison of ^{68}Ga-DOTATATE to other radiopharmaceuticals without other direct imaging

comparator but which were retained for reporting safety, toxicity and method of ^{68}Ga-DOTATATE synthesis and administration(*26-30*). Of the 17 included studies, 8 (47%) were retrospective,(*14, 17, 19, 21, 22, 26-28*) eight were prospective,(*15, 17, 18, 23, 25, 29-31*) and one(*20*) did not report their data collection method. Eight studies (47%) did not blind readers, 4 performed some level of blinding, and the remaining 5 did not report their blinding methods.

Comparison with ^{111}In-Octreotide or CI

A total of 169 patients were evaluated by both ^{68}Ga-DOTATATE and octreotide in the three direct comparison studies. By correspondence, Hofman(*14*) reported ^{68}Ga-DOTATATE PET/CT sensitivity and specificity in 40 patients of 100% and 86%, respectively. Deppen, et al,(*16*) reported ^{68}Ga-DOTATATE PET/CT sensitivity and specificity in 78 patients of 96% and 97%, respectively. Srirajaskanthan and colleagues(*15*) reported ^{68}Ga-DOTATATE sensitivity of 87% and specificity of 100% in 51 patients with negative or weak octreotide scan results. Pooled cancer prevalence among all 11 studies including any comparative conventional imaging with ^{68}Ga-DOTATATE PET/CT was 70%. In 10 of these, 5 had 100% of subjects with metastatic disease, 5 had a mix of malignant and benign patients, with all 10 reported per-patient results. Two studies(*22, 32*) reported results by region or organ and not by patient, and so were not included in our final meta-analysis because confirmation was not available for all areas of uptake.

Among the 10 remaining studies, with 465 patients, based upon a random effects model for ^{68}Ga DOTATATE PET/CT, the estimated sensitivity and specificity were 90.9% (95%CI: 81.4%, 96.4%) and 90.6% (95%CI: 77.8%, 96.1%), respectively (Fig. 2,

Forest Plots). Pooled estimates of sensitivity and specificity were not influenced by any

study characteristics, including study quality score, year of publication, having only

cancer cases or average age of participants. I^2, which is derived from Cochran's Q and

reports the percentage of variation attributable to heterogeneity, was significant for

sensitivity (65%) across the ten studies that reported results on a per-patient basis. No

heterogeneity in specificity was observed among the 5 studies (I^2=0%) with both

malignant and benign disease. However, both of these estimates of heterogeneity are

likely underpowered because of too few studies, and are only reported here for sake of

completeness.(33) A hierarchical summary ROC curve did not converge due to too few

studies.

Fig. 2: Forest plots with random effects estimates and individual study sensitivity and

specificity

Deek's funnel plot asymmetry test indicated no evidence for publication bias

(p=0.30) among the five studies reporting both sensitivity and specificity. A p-value

below 0.10 suggests possible publication bias; however, this bias estimate, with only

five studies, suffers from low power, possibly underestimating publication bias.

Publication bias was similar when including the additional 5 studies reporting only

sensitivity (p=0.26). It is important to note that the comparison standard for presence or

absence of disease differed across studies. Thus the estimates of sensitivity and

specificity of both ^{68}Ga-DOTATATE and octreotide are not highly precise. Accordingly,

the more robust measure of major or minor change in management is presented as a

better marker of the impact of these scans on patient care.

Toxicity

There was minimal toxicity reported in the original manuscripts of all studies, either a short statement indicating that no adverse events were observed, or no statement regarding toxicity. Email communication with the authors requesting more specific information on toxicity revealed additional information. Toxicity data for the use of ^{68}Ga-DOTATATE, the range of DOTATATE peptide mass used, and the injected activity range are summarized in Supplemental File 4. The number of patients receiving ^{68}Ga-DOTATATE, and whether the patients were receiving short-acting or long-acting octreotide medication at the time of the scan, are also shown. Only one study's administered peptide mass was over 50 µg,(29) with the lowest mass ranging from 2 - 13 µg(22). Activity was under 220 MBq except in one study reporting 165 - 243 MBq(14). Deppen,(16) Etchebehere(18) and Kunikowska(29) were the only investigators reporting adverse events (n=6). One subject had post-scan tachycardia resolving without treatment,(16) two had mild, unexplained symptoms determined by the local IRB to not be serious or related to the research,(18) two with a history of gastritis reported abdominal pain associated with ^{68}Ga-DOTATATE administration (effectively treated with an anti-spasmodic drug),(29) and the sixth subject(18) reported unilateral whole-body edema ipsilateral to the injected upper extremity, occurring within 24 hours of injection and resolving spontaneously in less than 48 hours, with no other sequelae, and not directly observed by medical staff. This last adverse event was determined by the local IRB to not be serious but possibly related to the research. Glucose testing among insulinoma patents found no changes in glucose levels(29).

Study quality scoring

Among the 12 studies comparing ^{68}Ga-DOTATATE to any other imaging, 6 (50%) were retrospective, 5 were prospective and 1 did not state the method of data collection. Four of the studies reported blinding of readers to other patient information, and five did not blind scan readers. Three studies did not report their methods of blinding (Supplemental file 3). Median quality score across the 17 studies was 7 (interquartile range; 6, 8). Quality varied from 11 of 13 QUADAS criteria in one study(23) to 3 of 13 quality criteria in 1 study(28). Five studies lacking comparative imaging information were included for toxicity and harm purposes only. Among 12 studies comparing ^{68}Ga-DOTATATE to other imaging modalities, the mean quality score was 7.8 (95%CI: 6.7, 9.1).

^{68}Ga-DOTATATE PET/CT Compared to Octreotide Imaging

Hofman, et al,(14) in a retrospective, blinded review of 59 patients (52 proven or suspected bronchial or GEP NETs and 7 neural crest/mesenchymal tumors) determined impact on care of ^{68}Ga-DOTATATE compared to octreotide and conventional imaging. Reports from previous CI (contrast-enhanced CT, MRI, ultrasound, plain-film radiographs and bone scintigraphy) were separately reviewed. ^{68}Ga-DOTATATE better demonstrated disease extent (100%) than octreotide (83%) and conventional (68%) imaging. Treatment change impact measured by change in intended treatment before vs. after ^{68}Ga-DOTATATE scanning was high (inter-modality) in 47%, moderate (intra-modality) in 10%, low in 41%, and not assessable in 2%. High impact included identifying candidates for potentially curative surgery, identifying nonsurgical candidates, and changing type of systemic treatment. Compared to CI, ^{68}Ga-DOTATATE imaging provided clinically significant information in 40 patients (56%),

typically by identifying greater extent of disease. Compared to octreotide SPECT/CT, ^{68}Ga-DOTATATE provided significant additional information in 33 of 40 (83%). On a per-lesion basis, ^{68}Ga-DOTATATE PET/CT revealed 90 additional tumor foci (bone (18), liver (17), pancreas (15), locoregional nodes (13), distant nodes (11), small bowel (8), peritoneum (4) and pleura (4)). ^{68}Ga-DOTATATE PET/CT had high clinical impact compared to conventional and octreotide imaging.

Srirajaskanthan, et al,(15) reported ^{68}Ga-DOTATATE PET/CT results in 51 patients with negative (35) or equivocal (16) octreotide SPECT scans, reported by anatomical region. The patients were selected from 312 (16.3%) patients with NET with a "Krenning score"(34) <2 (uptake less than normal liver). Verification was via three-phase CT or MRI. Forty-seven (92%) had evidence of tumor biochemically or by CI. Somatostatin analogs were not withdrawn in the 27 patients receiving these medications. Primary tumor sources were pulmonary (2), thyroid (2), thymus (2), pancreas (13), midgut (22), hindgut (2), paragangliomas (2), and unknown primary tumors(6). Previous treatments included surgery (9) and chemotherapy (10).

^{68}Ga-DOTATATE PET/CT was positive in 168/226 focal lesions (74.3%) confirmed with CI, significantly greater than octreotide SPECT (p < 0.001). Impact on treatment assessed retrospectively demonstrated that ^{68}Ga-DOTATATE had a major impact on 36 (71%). Four with negative ^{68}Ga-DOTATATE and octreotide scans were excluded from PRRT. Seven of 51 patients (14%) with tumor on ^{68}Ga-DOTATATE imaging but without symptoms began somatostatin analog treatment. Surgery was suggested in 4 (8%) patients based on potentially resectable disease confirmed with CI, but not seen with octreotide SPECT, although 1 declined surgery. ^{68}Ga-DOTATATE

imaging changed management in 70%. In 47 patients with evidence of tumor by MRI, CT, or biochemically, ^{68}Ga-DOTATATE PET/CT found disease in 41 (87.2%), with 39% referred for PRRT due to strong ^{68}Ga-DOTATATE uptake despite being misclassified on octreotide SPECT.

In a prospective study Deppen and colleagues(16) reported ^{68}Ga-DOTATATE PET/CT scanning in 97 patients with known or suspected NETs, 78 also having ^{111}In-DTPA-octreotide scans, and reported quantitative toxicology and systematic tracking of possible harms from ^{68}Ga-DOTATATE. ^{68}Ga-DOTATATE imaging was compared to planar (4%), SPECT (33%) and SPECT/CT (62%) ^{111}In-DTPA-octreotide scans. Though half of comparative ^{68}Ga-DOTATATE scans occurred > 180 days after the comparator ^{111}In-DTPA-octreotide scan, no difference was found in level of treatment change comparing time between scans. A limitation of toxicity testing was that 28 participants were missing some or all post-scan blood analyses.

Deppen, et al,(16) had three important findings. First, ^{68}Ga-DOTATATE was significantly more accurate (0.94; 95%CI: 0.89, 1.00) than octreotide imaging (0.82; 95%CI: 0.74, 0.90), p<0.02. Second, ^{68}Ga-DOTATATE imaging had major impact (inter-modality) on treatment decisions in 29 (37%) and minor (intra-modality) impact in 9 (12%) (Fig. 3). Third, there were no adverse events requiring treatment. One patient with a baseline heart rate of 87 had post-scan transient asymptomatic tachycardia (rate 112), spontaneously returning to normal sinus rhythm within an hour. Four patients had minor and transient asymptomatic changes in laboratory tests. ^{68}Ga-DOTATATE was equivalent or superior to ^{111}In-DTPA-octreotide imaging in all 78 patients.

Fig. 3: ^{111}In-DTPA-octreotide SPECT/CT (A) and ^{68}Ga-DOTATATE PET/CT (B) (maximum intensity projections shown) of a patient with liver metastases from small bowel NET. One metastasis was suspected on SPECT/CT (not shown). Nine liver metastases were found with PET/CT, changing the surgical plan. Findings surgically confirmed.

^{68}Ga-DOTATATE PET/CT compared to conventional imaging

Nine studies reported ^{68}Ga-DOTATATE compared with CI(*17, 19, 20, 25*) or with CI with other imaging including ^{68}Ga-DOTANOC(*22, 23*), ^{18}F-DOPA,(*24*) MRI, ^{99m}Tc-HYNIC-octreotide(*18*), or ^{18}F-fluorodoxyglucose(*21*) (Table 1). These studies, summarized in Supplemental File 5, vary widely in patient populations and study purpose. Five studies examined ^{68}Ga-DOTATATE accuracy in identifying metastatic disease(*18, 20-23*) .

DISCUSSION

Direct comparisons of octreotide and ^{68}Ga-DOTATATE imaging for diagnosis and staging in biased populations of NETs have been published. One unbiased but unpublished prospective study(*31*) found ^{68}Ga-DOTATATE significantly superior to octreotide in both diagnostic accuracy and impact on treatment. Limited published literature directly comparing ^{111}In-DTPA-octrotide to ^{68}Ga-DOTATATE imaging supports superiority of ^{68}Ga-DOTATATE PET/CT for diagnosis or reassessment of tumors with high somatostatin receptor expression. Available evidence also supports that ^{68}Ga-DOTATATE imaging often demonstrates tumor uptake in some patients with negative or equivocal octreotide scans, thereby identifying additional patients who might benefit from PRRT.(*35*) No significant harms were reported.

CONCLUSION

Reports comparing ^{68}Ga-DOTATATE PET/CT to ^{111}In-DTPA-octreotide and CI support the added value of ^{68}Ga-DOTATATE imaging with additional sites of tumor, including metastases and occult primaries often seen. The available evidence demonstrates, in mass dose of 125 micrograms or less, ^{68}Ga-DOTATATE has minimal toxicity. These reports have limitations from lack of consistent patient populations, prior treatment protocols and confirmation. Given the superior image quality, lower radiation dosimetry(*36*) and greater patient convenience (2 hours versus 2-3 days for octreotide imaging), ^{68}Ga-DOTATATE is clinically equivalent or superior to octreotide imaging and should be used where available.

REFERENCES

1.   Vinik AI, Woltering EA, Warner RR, et al. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas.* 2010;39:713-734.

2.   Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063-3072.

3.   Balon HR, Brown TL, Goldsmith SJ, et al. The SNM Practice Guideline for Somatostatin Receptor Scintigraphy 2.0. *J Nucl Med Technol.* 2011;39:317-324.

4.   Krenning EP, Bakker WH, Kooij PP, et al. Somatostatin receptor scintigraphy with indium-111-DTPA-D-Phe-1-octreotide in man: metabolism, dosimetry and comparison with iodine-123-Tyr-3-octreotide. *J Nucl Med.* 1992;33:652-658.

5.   Ambrosini V, Campana D, Tomassetti P, Fanti S. 68Ga-labelled peptides for diagnosis of gastroenteropancreatic NET. *Eur J Nucl Med Mol Imaging.* 2012;39:S52-60.

6.   Treglia G, Castaldi P, Rindi G, Giordano A, Rufini V. Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. *Endocrine.* 2012;42:80-87.

7.   Yang J, Kan Y, Ge BH, Yuan L, Li C, Zhao W. Diagnostic role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. *Acta Radiol.* 2013;55:389-398.

8.   Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* 2013;40:1770-1780.

9.   Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging.* 2014;4:426-434.

10.   Moher D, Liberati A, Tetzlaff J, Altman DG, Group tP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med.* 2009;151:264-269.

11.   Fontela PS, Pant Pai N, Schiller I, Dendukuri N, Ramsay A, Pai M. Quality and Reporting of Diagnostic Accuracy Studies in TB, HIV and Malaria: Evaluation Using QUADAS and STARD Standards. *PLoS One.* 2009;4:e7753.

12.   Whiting P, Rutjes A, Reitsma J, Bossuyt P, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003;3:25.

13.   U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. In: Services USDoHaH, ed. Vol Publication No 09-5410: NIH; 2009.

14.   Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol.* 2012;56:40-47.

15.   Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, Bomanji J. The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. *J Nucl Med.* 2010;51:875-882.

16.   Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of 68Ga-DOTATATE PET/CTfor diagnosis, staging and treatment management of neuroendocrine tumors. *J Nucl Med.* In press..

17.   Alonso O, Rodriguez-Taroco M, Savio E, Bentancourt C, Gambini JP, Engler H. (68)Ga-DOTATATE PET/CT in the evaluation of patients with neuroendocrine metastatic carcinoma of unknown origin. *Ann Nucl Med.* 2014;28:638-645.

18.   Etchebehere EC, de Oliveira Santos A, Gumz B, et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-Octreotide SPECT/CT, and Whole-Body MR Imaging in Detection of Neuroendocrine Tumors: A Prospective Trial. *J Nucl Med.* 2014;55:1598-1604.

19.   Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. The Role of 68Ga-DOTATATE PET/CT in Suspected Neuroendocrine Tumors. *J Nucl Med.* 2012;53:1686-1692.

20.   Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. Neuroendocrine tumor recurrence: diagnosis with 68Ga-DOTATATE PET/CT. *Radiology.* 2014;270:517-525.

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

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

23.   Wild D, Bomanji JB, Benkert P, et al. Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT Within Patients with Gastroenteropancreatic Neuroendocrine Tumors. *J Nucl Med.* 2013;54:364-372.

24. Haug A, Auernhammer CJ, Wangler B, et al. Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2009;36:765-770.

25. Lastoria S, Marciello F, Faggiano A, et al. Role of Ga-DOTATATE PET/CT in patients with multiple endocrine neoplasia type 1 (MEN1). *Endocrine.* 2015.

26. Lapinska G, Bryszewska M, Fijolek-Warszewska A, Kozlowicz-Gudzinska I, Ochman P, Sackiewicz-Slaby A. The diagnostic role of 68Ga-DOTATATE PET/CT in the detection of neuroendocrine tumours. *Nucl Med Rev Cent East Eur.* 2011;14:16-20.

27. Brogsitter C, Zophel K, Hartmann H, Schottelius M, Wester HJ, Kotzerke J. Twins in spirit part II: DOTATATE and high-affinity DOTATATE--the clinical experience. *Eur J Nucl Med Mol Imaging.* 2014;41:1158-1165.

28. Ilhan H, Fendler W, Cyran C, et al. Impact of 68Ga-DOTATATE PET/CT on the Surgical Management of Primary Neuroendocrine Tumors of the Pancreas or Ileum. *Annals of Surgical Oncology.* 2015;22:164-171.

29. Kunikowska J, Pawlak D, Kolasa A, Mikolajczak R, Krolicki L. A Frequency and Semiquantitative Analysis of Pathological 68Ga DOTATATE PET/CT Uptake by Primary Site-Dependent Neuroendocrine Tumor Metastasis. *Clin Nucl Med.* 2014;39:855-861.

30. Has Simsek D, Kuyumcu S, Turkmen C, et al. Can complementary 68Ga-DOTATATE and 18F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? *J Nucl Med.* 2014;55:1811-1817.

31. Walker RC. Imaging and Treatment of Neuroendocrine Tumors. *Nuclear Molecular Imaging and Therapy: Focus on Value.* Johns Hopkins University School of Medicine, Baltimore MD; 2014.

32. Etchebehere EC, de Oliveira Santos A, Gumz B, et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-Octreotide SPECT/CT, and Whole-Body MR Imaging in Detection of Neuroendocrine Tumors: A Prospective Trial. *J Nucl Med.* 2014;55:1598-1604.

33. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Introduction to Meta-Analysis.* 1 ed: Wiley; 2009.

34. Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. *J Clin Oncol.* 2005;23:2754-2762.

35. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol.* 2008;26:2124-2130.

36. Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of 68Ga-DOTATATE. *J Nucl Med.* 2013;54:855-860.
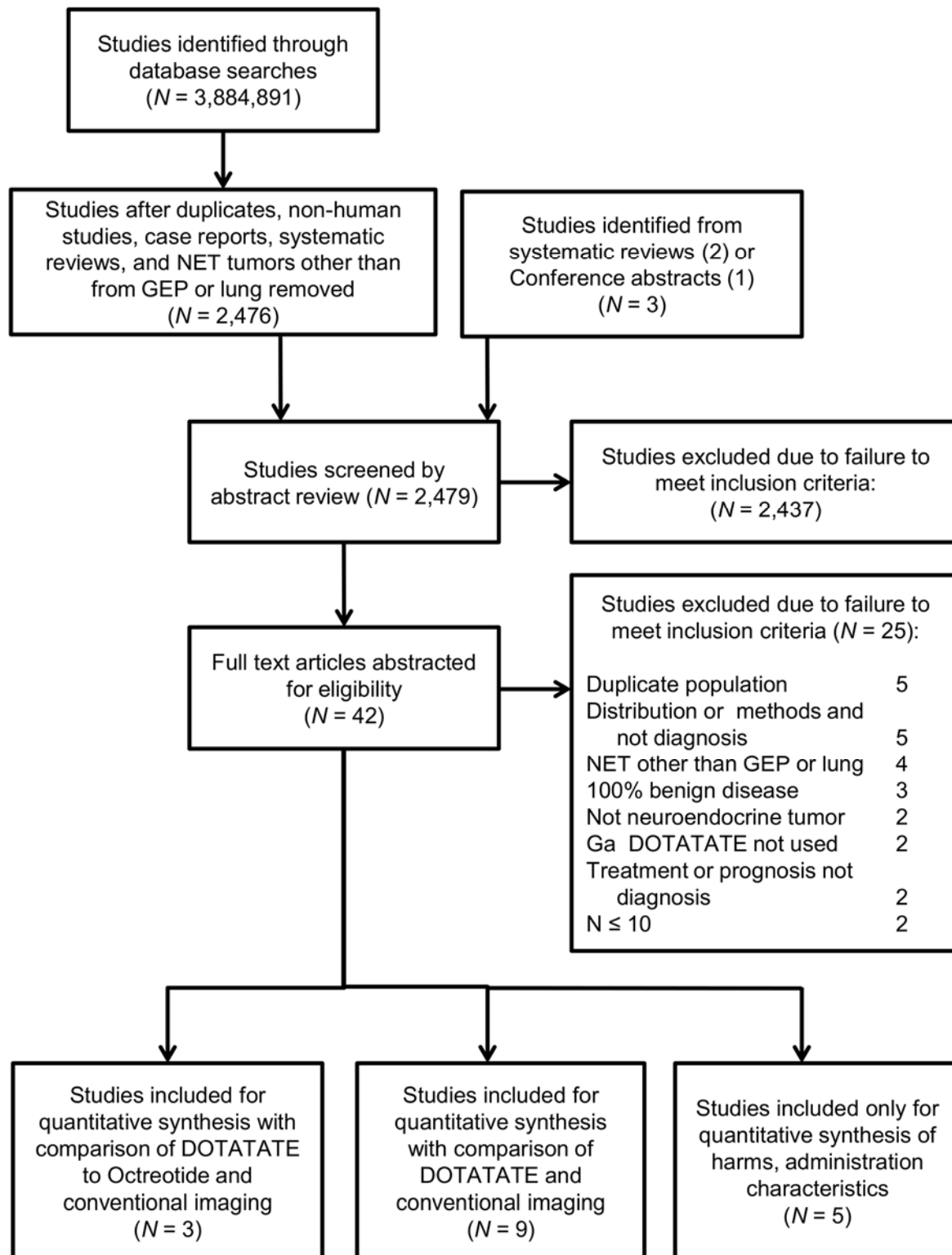
FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

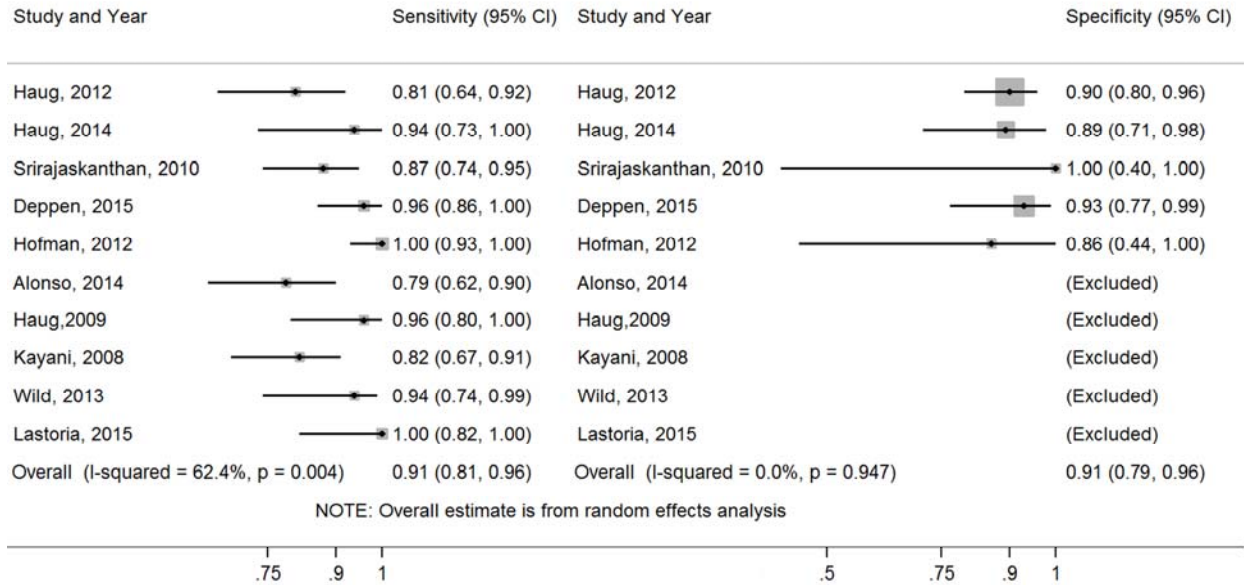(PRISMA) diagram of studies from systematic review.

Study and Year		Sensitivity (95% CI)	Study and Year		Specificity (95% CI)
Haug, 2012		0.81 (0.64, 0.92)	Haug, 2012		0.90 (0.80, 0.96)
Haug, 2014		0.94 (0.73, 1.00)	Haug, 2014		0.89 (0.71, 0.98)
Srirajaskanthan, 2010		0.87 (0.74, 0.95)	Srirajaskanthan, 2010		1.00 (0.40, 1.00)
Deppen, 2015		0.96 (0.86, 1.00)	Deppen, 2015		0.93 (0.77, 0.99)
Hofman, 2012		1.00 (0.93, 1.00)	Hofman, 2012		0.86 (0.44, 1.00)
Alonso, 2014		0.79 (0.62, 0.90)	Alonso, 2014		(Excluded)
Haug, 2009		0.96 (0.80, 1.00)	Haug, 2009		(Excluded)
Kayani, 2008		0.82 (0.67, 0.91)	Kayani, 2008		(Excluded)
Wild, 2013		0.94 (0.74, 0.99)	Wild, 2013		(Excluded)
Lastoria, 2015		1.00 (0.82, 1.00)	Lastoria, 2015		(Excluded)
Overall (I-squared = 62.4%, p = 0.004)		0.91 (0.81, 0.96)	Overall (I-squared = 0.0%, p = 0.947)		0.91 (0.79, 0.96)

NOTE: Overall estimate is from random effects analysis

Figure 2: Forest plots with random effects estimates and individual study sensitivity and specificity

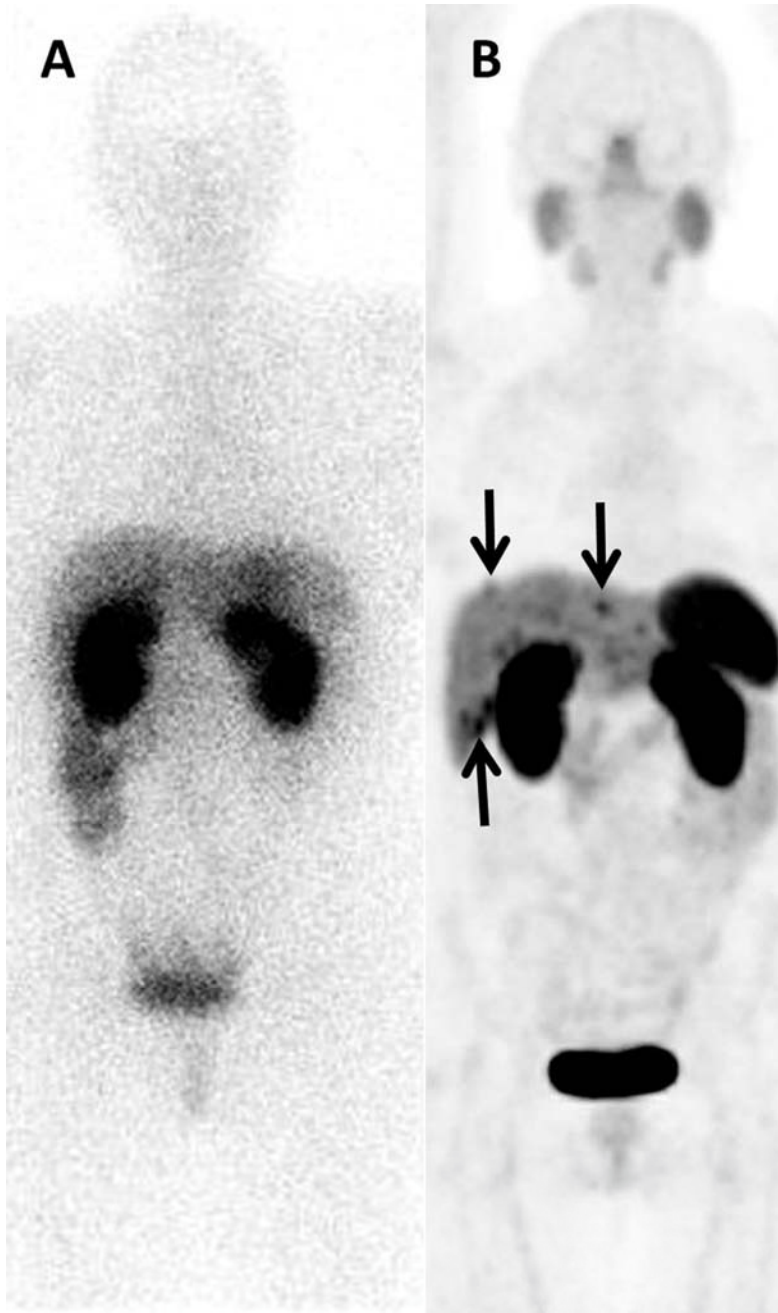**Figure 3**: ^{111}In-DTPA-octreotide SPECT/CT (A) and ^{68}Ga-DOTATATE PET/CT (B)

(maximum intensity projections shown) of a patient with suspected recurrence of small

bowel NET in the liver. One metastasis was suspected on SPECT/CT (not shown).

Nine liver metastases were found with PET/CT, resulting is a change in surgical plan.

Findings confirmed at surgery.

Table 1 Study Characteristics

Study	Quality Score	Cancer/Benign	Sensitivity (95%CI)	Specificity (95%CI)	Patient Population	Treatment Management
Studies comparing 68Ga-DOTATATE and ^{111}In-Octreotide to conventional imaging						
Hofman, 2012	8	N=59, 40 had both scan modalities (cancer 52/benign 7)	100 (93, 100)	86 (43, 100)	Clinical need nonconsecutive patients. 52 proven or suspected bronchial or GEP NETs and 7 other tumors, 40 had both DOTATATE and octreotide scans.	DOTATATE provided additional clinically significant information in 33 (83%) patients. Bone metastasis (18 patients) was the most common differential result.
Srirajaskanthan, 2010	7	47/4	87 (74, 95)	100 (40, 100)	Patients with negative or equivocal octreotide scans; 27 receiving somatostatin analog medication.	Major impact on 36 (71%) with PPRT (n=20) treatment being the most common change.
Deppen, in press	9	N=97 DOTATATE scans, 78 also with octreotide scans (cancer 50/benign 28)	96 (86, 100)	93 (77, 99)	Consecutive patients prospectively enrolled comparing the imaging modalities. 76 proven or suspected GEP, intestinal or bronchial NETs.	DOTATATE scans resulted in major (36%) or minor (14%) treatment changes. Octreotide false negative in 14.
Studies comparing 68Ga-DOTATATE to conventional imaging						
Alonso, 2014	7	29/0	79 (62, 90)	NA	Evaluation of patients with metastatic NET from unknown primaries not seen by CI.	No statements regarding treatment change. Primary found in 17 (59%). DOTATATE found greater extent of tumor in 6 more (21%)
Etchebehere, 2014	8	N=19 results reported by body region	100 (NA)[a]	67 (NA)[a]	DOTATATE compared with whole-body MRI and ^{99m}Tc-HYNIC-Octreotide SPECT/CT in proven NET patients with suspected recurrence.	No statements regarding treatment change. DOTATATE and MRI combined found all primary and significant metastatic tumor. DOTATATE found bone

						metastases missed by MRI and SPECT/CT.
Haug, 2014	7	18/27[b]	94 (72, 100)	89 (71, 98)	Re-staging of post-resection NETs by DOTATATE and CI.	No statements regarding treatment change.
Haug, 2012	9	36/68[c]	81 (64, 92)	90 (80,96)	Staging of patients by presentation type: symptomatic, pathologically proven and suspicious imaging.	No statements regarding treatment change.
Haug, 2009	7	25/0	96 (80, 100)	NA	Metastatic disease in 14 GEP, 6 Lung, 4 unknown primary, and 1 paranasal sinus primary.	Superior sensitivity to F18-DOPA, other changes to treatment not stated compared to CI.
Kayani, 2008	8	38/0	82 (67, 91)	NA	Metastatic disease in 28 GEP, 6 Lung, and 4 metastatic NETs with unknown primary. Compared to FDG-PET.	Change in PPRT therapy in 4 with low DOTATATE uptake. Complimentary to FDG PET regarding tumor grade.
Lastoria, 2015	7	18/0	100 (82, 100)	NA	11 GEP NETs. MEN1 syndrome in all patients	No statements regarding treatment impact.
Poeppel, 2013	6	40/0	NA	NA	All proven GEP NETs with and without recurrence. DOTATATE compared to DOTATOC. All lesions verified via CT or follow-up.	No difference in management impact between DOTATATE and DOTANOC.
Wild, 2013	11	18/0	94 (74, 99)	NA	Biopsy proven metastatic GEP with CT or MRI imaging also available. All patients had both DOTATATE and DOTANOC scans.	No difference in management impact between DOTATATE and DOTANOC. Change in surgical plan in 3 patients.

a for all solid organs, 100% sensitive and specific for musculoskeletal metastases.

b GEP tumors, unblinded reviewers

c included 12 without NET tumor.