
**PET Recommendation Report 19**

## A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

# Gallium-68 PET Imaging in Neuroendocrine Tumours

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PET Recommendation Report 19

# Gallium-68 PET Imaging in Neuroendocrine Tumours

## Section 1: Recommendations and Key Evidence

**OBJECTIVES**

To provide a summary of evidence surrounding the clinical utility of Gallium-68 ($^{68}$Ga) positron emission tomography (PET) imaging in patients with neuroendocrine tumours (NETs) and recommendations for their use in Ontario.

**TARGET POPULATION**

Adult and pediatric patients with suspected or diagnosed well-differentiated NETs.

**INTENDED USERS**

This recommendation report is intended to guide the Ontario PET Steering Committee with respect to the development of indications in the context of the patient management pathway. This recommendation report may also be useful to inform clinicians who are involved in the care of patients with NETs.

**RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE**

| **Recommendation 1** |
|---|
| **$^{68}$Ga-DOTA-TATE/-TOC/-NOC PET or PET/computed tomography (CT) is recommended for the initial diagnosis of adult patients with clinical (e.g., signs, symptoms) and biochemical (e.g., markers) suspicion of NETs but for whom conventional imaging is negative or equivocal or for whom biopsy is not easily obtained.** |
| ***Qualifying Statements for Recommendation 1*** |
| • PET or PET/CT functions as a supplement to and does not replace biopsy for establishing a definite diagnosis.<br>• It is unknown whether pediatric patients would benefit from PET or PET/CT since there is a lack of evidence to support making any recommendation for this specific population. |
| ***Key Evidence for Recommendation 1*** |
| • Six studies assessed the sensitivity and specificity of PET or PET/CT for the initial diagnosis of NETs [1-6]. The sensitivity and specificity on a per-patient based analysis ranged from 81% to 100%, and 85% to 100%, respectively, with a summarized sensitivity of 91% (95% confidence interval [CI], 85% to 94%) and specificity of 94% (95% CI, 86% to 98%). |
| ***Interpretation of Evidence for Recommendation 1*** |
| The meta-analysis of six studies showed that PET or PET/CT is highly sensitive and specific for evaluating patients with a suspicion of NETs at initial diagnosis. PET or PET/CT does not negate the need for a biopsy as biopsy remains the gold standard for preventing unnecessary additional tests or procedures due to the potential for false-positive scans. In addition, other disease-specific information (e.g., ki-67, differentiation) can be obtained from a tissue biopsy that is not determinable from PET or PET/CT. Poorly differentiated NETs often have reduced expression of somatostatin receptors that may lead to false-negative scans; even so, downstream testing would not be considered without other corroborating data. Overall, study quality was limited by the uncertainties surrounding the blinded interpretation of the index test (PET or PET/CT) and reference standard (histology and/or follow-up). Unclear risk may be a consequence of incomplete reporting; however, it is unknown whether this would have an impact on the results or conclusions of the study. |

**Recommendation 2**

**$^{68}$Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with localized primary NETs and/or limited metastasis where definitive surgery is planned.**

**$^{68}$Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for determining somatostatin receptor status and suitability for peptide receptor radionuclide therapy.**

**$^{68}$Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with NETs where detection of occult disease will alter the treatment options and decision making.**

***Qualifying Statements for Recommendation 2***

- PET or PET/CT may be superior to octreoscan for all the stated indications.
- It is unknown whether pediatric patients would benefit from PET or PET/CT since there is a lack of evidence to support making any recommendation for this specific population.

***Key Evidence for Recommendation 2***

- In the 10 direct-comparison studies, the sensitivity of PET or PET/CT for detecting primary and/or metastatic lesions ranged from 78.3% to 100%, whereas the specificity ranged from 50% to 100% [2,7-15].
- Naswa et al [11] demonstrated that $^{68}$Ga-DOTA-NOC PET/CT was better than conventional imaging (contrast-enhanced CT [CeCT], magnetic resonance imaging, ultrasound) in detecting both the primary tumour (sensitivity, 78.3% versus 63.8%, $p<0.001$) and metastases (sensitivity, 97.4% versus 81.8%, $p<0.001$), while maintaining high specificities.
- Albanus et al [14] reported $^{68}$Ga-DOTA-TATE PET/CT to be more sensitive and more specific than CeCT in detecting lymph node metastases (sensitivity, 92% versus 64%, $p=0.0156$; specificity, 83% versus 59%, $p=0.0386$) and bone metastases (sensitivity, 100% versus 47%, $p=0.0039$; specificity, 89% versus 49%, $p=0.0004$). $^{68}$Ga-DOTA-NOC PET/CT was also more specific than CeCT for the detection of pulmonary metastases (95% versus 82%, $p=0.0313$), with equal sensitivity.
- Overall, change in management occurred in 45% (95% CI, 36% to 55%) of cases, with the majority of the changes involving surgical planning and patient selection for peptide receptor radionuclide therapy [7,10,11,13,16-20].

***Interpretation of Evidence for Recommendation 2***

Due to the heterogeneity of the studies in terms of diagnostic performance measure for which PET or PET/CT was indicated, the Working Group members considered a change or impact in decisions in patient management to be the most appropriate outcome. There remains the possibility that PET or PET/CT may demonstrate false-positive results that would lead to inappropriate changes in management. Nonetheless, PET or PET/CT provides superior evaluation of disease when conventional imaging is equivocal. This is particularly true in instances where a biopsy is not easily obtained.

**Recommendation 3**

**There is no recommendation regarding the use of $^{68}$Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the assessment of treatment response for NETs.**

***Qualifying Statements for Recommendation 3***

- PET or PET/CT may be a good early predictor of disease progression by identifying new metastases that developed during therapy.

***Key Evidence for Recommendation 3***

- In one study, 46 patients with advanced NETs were investigated before and after two to

| |
|---|
| seven cycles of $^{90}$Y-DOTA-TOC or $^{177}$Lu-DOTA-TATE. According to visual response criteria, $^{68}$Ga-DOTA-TOC PET showed no advantage over CT for assessing response to therapy (accuracy, 91.3% versus 78.3%, respectively, p=0.27) [22]. |
| ***Interpretation of Evidence for Recommendation 3*** |
| Only one study evaluated the role of PET or PET/CT in the assessment of response after therapy; therefore, the evidence is currently insufficient to support the use of PET or PET/CT in this setting. Since the study utilized a dedicated PET scanner without a CT component, it is uncertain whether the integration of PET with low-dose CT (PET/CT) would significantly impact the diagnostic yield of the test. |
| **Recommendation 4** |
| **There is no recommendation regarding the use of $^{68}$Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the routine surveillance of NETs.** |
| ***Qualifying Statements for Recommendation 4*** |
| • PET or PET/CT should not be used in place of conventional imaging for routine monitoring of asymptomatic patients with no evidence of neuroendocrine activity. |
| ***Key Evidence for Recommendation 4*** |
| • There were no studies identified that met the study selection criteria examining PET or PET/CT in the routine surveillance of NETs. |
| ***Interpretation of Evidence for Recommendation 4*** |
| The evidence is currently insufficient to support the use of PET or PET/CT in this setting. |

**IMPLEMENTATION CONSIDERATIONS**

The Working Group members considered these recommendations to be aligned with current practices and patterns of care as well as the desire of the patient community for extended access to $^{68}$Ga-DOTA-TATE/-TOC/-NOC PET/CT. Requests from physicians for the provision of this imaging modality for patients will be streamlined in a registry setting. As per all PET scanning services in Ontario, requests for a PET scan for clinical scenarios outside of the recommended indications can be made through the PET Access Program. Each referral is assessed on a case-by-case basis by a panel of experts.

**FUTURE RESEARCH**

There currently are insufficient data displaying improved outcomes in the routine use of $^{68}$Ga-DOTA-TATE/-TOC/-NOC PET/CT in surveillance and to assess treatment response. These indications should be reviewed as new data become available in the future.

# Gallium-68 PET Imaging in Neuroendocrine Tumours:

## Section 2: Recommendation Report Methods Overview

*This section summarizes the methods used to create the guideline. For the systematic review, see Section 3.*

### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

### JUSTIFICATION FOR RECOMMENDATION REPORT

To determine the role of the use of Gallium-68 ($^{68}$Ga) positron emission tomography (PET) for neuroendocrine tumours (NETs), and to inform expansion of the use of $^{68}$Ga PET for this patient population in Ontario.

### RECOMMENDATION REPORT DEVELOPERS

This recommendation report was developed by a Working Group consisting of a medical oncologist and a radiation oncologist who treat NETs patients, a radiologist with expertise in PET imaging, and a health research methodologist at the request of the Ontario PET Steering Committee.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations and responding to comments received during the document review process. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

### RECOMMENDATION REPORT DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [23,24]. For Recommendation Reports, this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by a methodology experts, and final approval by the Sponsoring Committee.

The PEBC uses the AGREE II framework [25] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline

development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

**Search for Existing Guidelines**

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework [26], or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. The following sources were searched up to May 9, 2017 for existing guidelines that were based on a systematic review with well-described methods and addressed the research questions:

- Practice guideline databases: Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument [25].

## RECOMMENDATION REPORT REVIEW AND APPROVAL

**Internal Review**

The recommendation report was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval.

**Report Approval by the Ontario PET Steering Committee and the Neuroendocrine Tumours Advisory Committee**

After internal review, the report was presented to the Ontario PET Steering Committee. The committee reviewed and formally approved the document on May 17, 2018. The report was presented to the Neuroendocrine Tumours Advisory Committee on September 26, 2018 and feedback obtained was incorporated in the final revision.

## ACKNOWLEDGEMENTS

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- Melissa Brouwers and Xiaomei Yao for providing feedback on draft versions.
- Karthik Kannan for conducting a data audit.
- Sara Miller for copy editing.

# Gallium-68 PET Imaging in Neuroendocrine Tumours

## Section 3: Systematic Review

**INTRODUCTION**

NETs are a heterogeneous group of neoplasms that arise from cells of the endocrine and nervous systems. These tumours can originate from various areas of the body but are most commonly found in the gastrointestinal or bronchopulmonary system [27]. NETs can be functioning with hormone secretion and often produce symptoms, or can be nonfunctioning. NETs commonly present with non-specific symptoms such as bloating and weight loss, and can be difficult to detect or diagnose. NETs have historically been considered rare malignancies; however, recent data from Ontario are suggesting that the incidence of NETs has increased substantially in a 15-year period; from 2.48 cases per 100,000 per year in 1994 to 5.86 cases per 100,000 per year in 2009 [28].

Given the ambiguous clinical manifestations of NETs, accurate assessment of the primary tumour and the extent of the metastatic spread can be challenging. A qualitative study conducted among NETs patients in Ontario expressed considerable frustration at a diagnostic delay [29]. Globally, NETs patients have also expressed concerns with their care including diagnostic delays and lack of access to modern imaging for NETs [30]. Presently, the diagnostic work-up often begins with physical examination and laboratory testing for specific biochemical markers; in most cases, these biochemical markers only present in the minority of patients with functional disease. Traditional radiological imaging has included computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US). Many NETs may be characterized by a spectrum of overexpression of somatostatin receptors on the cell surface; functional imaging with radiolabeled somatostatin analogues, namely, octreotide scanning has been proven to be a component in the routine investigation of these patients. The introduction of $^{68}$Ga-labeled somatostatin analogues ($^{68}$Ga-DOTA-TOC, $^{68}$Ga-DOTA-TATE, and $^{68}$Ga-DOTA-NOC) for PET/CT has quickly emerged as a promising alternative for diagnosing, staging, and follow-up of NETs. The European Society for Medical Oncology guidelines Working Group recommended that PET/CT using $^{68}$Ga-DOTA-TOC/-NOC/-TATE should be included in the preoperative staging and in the follow-up of neuroendocrine gastro-entero-pancreatic tumours [31]. The 2017 Version 2 of the National Comprehensive Cancer Network Treatment Guidelines for NETs also included $^{68}$Ga-DOTA-TATE PET/CT as a somatostatin receptor-based imaging option for use during the evaluation and work-up of NETs as appropriate. However, somatostatin receptor-based imaging and fluorodeoxyglucose PET/CT are not recommended for routine surveillance [32]. Most recently, the Society of Nuclear Medicine and Molecular Imaging has released appropriate use criteria (AUC) for somatostatin receptor PET imaging in NETs. This document advocates 12 scenarios where the use of $^{68}$Ga PET imaging is appropriate based on a multidisciplinary panel RAND/UCLA analysis with an appropriateness score for each indication reflecting the paucity of published data as well as clear outcome objectives when considering this topic [33].

Despite the advantages $^{68}$Ga scans can offer in terms of cost, patient time, improved image resolution, and higher sensitivity, current access to this service is limited to two sites in Canada (*Centre hospitalier universitaire de Sherbrooke* in Sherbrooke, Quebec and as part of the Ontario PRRT Consortium trial conducted at Princess Margaret Hospital, Sunnybrook Health Sciences, Juravinski and London Health Sciences). There has been considerable uptake of this technology reflecting its overall superiority over octreotide scanning in most scenarios. Consequently, along with a rapid increase in physician requests for these scans and

considerable demand for this imaging modality among patients, there is a need to provide broader access in Ontario. The purpose of this report is to provide a summary of evidence to inform recommendations regarding the role of $^{68}$Ga PET or PET/CT in the initial diagnosis, staging/restaging, response evaluation, and routine surveillance of patients with NETs.

## OBJECTIVES AND RESEARCH QUESTIONS

This Working Group developed the following objectives for this guideline in consultation with the Ontario PET Steering Committee.

- To provide a synthesis and summary of evidence surrounding the clinical utility of $^{68}$Ga PET imaging in patients with NETs.

From these objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives.

- What benefit to clinical management does PET or PET/CT contribute to the initial diagnosis of NETs?
- What benefit to clinical management does PET or PET/CT contribute to the staging and restaging of NETs?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for NETs?
- What benefit to clinical management does PET or PET/CT contribute to the routine surveillance of NETs?

## METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

### Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. The search was aimed at finding a review that covered the research questions and could be used, at least in part, as the evidentiary basis for this recommendation report. The electronic databases MEDLINE (1946 to May Week 2 2017), EMBASE (1974 to 2017 Week 19), and Cochrane Database of Systematic reviews (2005 to May 9, 2017) were searched through OVID. See Appendix 2 for the search strategy.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [34] tool to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

### Search for Primary Literature

If no eligible systematic reviews were identified, a primary search of the literature was conducted and described below.

#### *Literature Search Strategy*

The primary literature was searched using MEDLINE (1946 to May Week 2 2017) and Embase (1974 to 2017 Week 19) databases through OVID. Details of the literature search can be found in Appendix 2. In addition, reference lists from relevant systematic reviews and primary literature were scanned for potentially useful studies.

***Study Selection Criteria and Process***

*Inclusion Criteria*

1. Published as a full-text article in a peer-reviewed journal.
2. Evaluated the use of PET or PET/CT with $^{68}$Ga-DOTA-TATE/-TOC/-NOC.
3. Post-surgical or post-biopsy histology, clinical follow-up, or radiologic follow-up were used as the reference standard.
4. Reported on at least one of the following outcomes:
    - Numeric data on diagnostic performance (e.g., sensitivity, specificity, positive predictive value, negative predictive value, accuracy).
    - Metrics representing change or impact on clinical management decisions.
    - Survival data.
5. Included ≥12 patients for prospective studies or ≥50 patients for retrospective studies.

*Exclusion Criteria*

1. Studies that specifically looked for unknown primary in NETs.
2. Conference abstracts, literature or narrative reviews, letters, editorials, historical articles, or commentaries.
3. Single case reports or case series.
4. Reports published in a language other than English.

A review of the titles and abstracts that resulted from the search was conducted independently by one reviewer, as were the items that warranted full-text review.

***Data Extraction and Assessment of Study Quality and Potential for Bias***

One reviewer extracted data from the included studies. For each article, the principal author, publication year, country of origin, study design, number of patients, age, sex, type of PET device and tracer, method of image analysis, conventional imaging performed, and reference standard criteria, as well as the outcomes of interest were recorded. All extracted data and information were audited by an independent auditor for accuracy and completeness. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [35] tool was used to evaluate the risk of bias.

**Synthesizing the Evidence**

Data were summarized in evidence tables and described in the text. When clinically homogenous results from two or more studies and sufficient data were available, a bivariate, random-effects model was used to produce summary estimates of sensitivity and specificity with 95% confidence intervals (CIs) and to plot the summary receiver operating characteristic (SROC) curve with 95% confidence region. This model incorporates any correlation that might exist between sensitivity and specificity and accounts for the estimated variability among the studies [36]. Statistical analyses were performed with STATA version 11.2 using the metandi command and the metaprop command with Freeman-Tukey double arcsine transformation.

**RESULTS**

**Search for Existing Clinical Practice Guidelines and Systematic Reviews**

A search for existing guidelines did not yield an appropriate source document on which to build an evidence base. The search for existing systematic reviews identified five publications [37-41] that were considered relevant after title and abstract screening. However, upon full-text review, none of the systematic reviews reported separate results for

each indication that could be used to address any of the research questions and therefore were not discussed further. As such, the AGREE II instrument and AMSTAR tool were not used.

**Search for Primary Literature**

***Literature Search Results***

A search for primary literature was conducted and a total of 1660 unique citations were identified from the electronic searches, of which 1602 were excluded after a review of titles and abstracts. Fifty-eight citations were considered as candidates, but upon full-text review, 36 did not meet the inclusion criteria. Finally, the remaining 22 studies were included in this systematic review. No studies were found that met the study selection criteria examining the clinical utility of $^{68}$Ga PET imaging in the pediatric NETs population. See Appendix 3 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

***Study Design and Quality***

Ten studies enrolled patients prospectively [2,7-12,16,19,22], while 12 studies were retrospective outcomes review [1,3-6,13-15,17,18,20,21]. PET/CT scans were acquired in 20 studies [1,3-21] and PET scans in 2 studies [2,22]. The number of patients included in the studies ranged from 15 to 728. Details of the study characteristics are reported in Table 3-1. The 22 studies were assessed according to the four QUADAS-2 domains (Appendix 4). All studies were judged to have low concerns regarding applicability. For the domain relating to risk of bias, one study [17] was judged to have high risk in patient selection where medullary thyroid carcinomas were excluded from the analysis. Moreover, due to incomplete reporting in almost one-half of the studies [1,3-6,13,17,18,20,21], readings for the index tests (e.g., PET or PET/CT, conventional imaging) were unclear as to whether they were interpreted without the knowledge of the reference standard (e.g., histology, clinical/imaging follow-up, or consensus from multidisciplinary tumour board). In the same way, most of the studies lacked information about whether the reference standard results were interpreted without the knowledge of the index test results [1,3-6,8-15,17-21]. No studies were assessed as being at risk for bias in flow and timing. According to the GRADE criteria [42], the overall results are precise and there is no suspicion of relevant publication bias. However, there are problems with indirectness due to the lack of direct comparisons between the index tests as well as inconsistency due to significant heterogeneity for the outcome measures. On the whole, the quality of the evidence was judged to be low to moderate.

**Table 3-1. Studies selected for inclusion.**

| Study, year | Country | Study type | No. of pts | Mean age | Sex (M/F) | Device | Image analysis | Reference standard |
|---|---|---|---|---|---|---|---|---|
| Ambrosini et al, 2012 [1] | Italy | R | 131 | NA | NA | PET/CT | V | Histology, F-U |
| Gabriel et al, 2007 [2] | Austria | P | 84 | 58.2 | 48/36 | PET | V | Histology, F-U |
| Haidar et al, 2017 [3] | Lebanon, UK | R | 445 | 54 | 248/197 | PET/CT | NA | Histology, F-U |
| Haug et al, 2012 [4] | Germany | R | 104 | 58 | 52/52 | PET/CT | V | Histology, F-U |
| Sharma et al, 2014 [5] | India | R | 62 | 34.3 | 38/24 | PET/CT | V, SQ | Histology, F-U |
| Sharma et al, 2014 [6] | India | R | 164 | 42.5 | 90/74 | PET/CT | V | Histology, F-U |
| Deppen et al, 2016 [7] | US | P | 78 | 53.4 | 29/49 | PET/CT | V | Histology, MDTB |
| Etchebehere et al, 2014 [8] | Brazil | P | 19 | 54.3 | 10/9 | PET/CT | V | Histology, F-U, MDTB |
| Yamaga et al, 2017 [9] | Brazil | P | 15 | 43.6 | 6/9 | PET/CT | V | Histology, F-U |
| Schraml et al, 2013 [10] | Germany | P | 51 | 57 | 26/25 | PET/CT | V | Histology, F-U |
| Naswa et al, 2011 [11] | India | P | 109 | 50* | 58/51 | PET/CT | V, SQ | Histology, F-U |
| Van Binnebeek et al, 2016 [12] | Belgium | P | 53 | 59 | 23/30 | PET/CT | V | Histology, F-U |
| Srirajaskanthan et al, 2010 [13] | UK | R | 51 | 55.5 | 27/24 | PET/CT | V | Histology, F-U |
| Albanus et al, 2015 [14] | Germany | R | 54 | 64* | 26/28 | PET/CT | V, SQ | F-U |
| Ambrosini et al, 2010 [15] | Italy | R | 223 | 58 | 107/116 | PET/CT | V | F-U |
| Herrmann et al, 2015 [16] | US | P | 88 | 59 | 38/50 | PET/CT | V | Pre-/post-PET survey |
| Haug et al, 2014 [17] | Germany | R | 63 | 58 | 34/29 | PET/CT | V | Histology, F-U |
| Ambrosini et al, 2010 [18] | Italy | R | 90 | 58 | 54/36 | PET/CT | V | F-U |
| Frilling et al, 2010 [19] | Germany | P | 52 | 52 | 25/27 | PET/CT | V, SQ | Histology, F-U, MDTB |
| Skoura et al, 2016 [20] | UK | R | 728 | 54 | 340/388 | PET/CT | V | Histology, F-U, MDTB |
| Sharma et al, 2015 [21] | India | R | 90 | NA | NA | PET/CT | V, SQ | Histology, F-U |
| Gabriel et al, 2009 [22] | Austria | P | 46 | 59.2 | 29/17 | PET | V, SQ | F-U |

**Abbreviations:** CT, computed tomography; F, female; F-U, clinical/imaging follow-up; M, male; MDTB, multidisciplinary tumour board; NA, not available; P, prospective; PET, positron emission tomography; pts, patients; R, retrospective; SQ, semiquantitative; V, visual

*Median age

***Diagnosis***

In the initial diagnosis of NETs, six studies assessed the sensitivity and specificity of PET or PET/CT [1-6]. Patients were examined by PET or PET/CT for suspected NETs based on clinical features, elevated levels of biochemical markers, conventional imaging suggestive of NETs, or a combination of these conditions. While most studies included patients with various sites of suspected NETs [1-4,6], one study evaluated only patients with suspicion of pheochromocytoma [5]. PET or PET/CT was imaged using $^{68}$Ga-DOTA-NOC in four studies [1,3,5,6], and $^{68}$Ga-DOTA-TOC/-TATE in each of the other two studies, respectively [2,4] (Table 3-2). The sensitivity on a per-patient based analysis ranged from 81% to 100%, with a pooled estimate of 91% (95% CI, 85% to 94%) (Figure 3-1). Likewise, the specificity ranged from 85% to 100%, with a pooled estimate of 94% (95% CI, 86% to 98%) (Figure 3-2). The SROC curve for the combined studies is presented in Figure 3-3. Direct imaging comparator was reported for octreotide scan (sensitivity, 50%; specificity, 89%) and CT (sensitivity, 75%; specificity, 89%) in one study [2].

**Table 3-2: Diagnostic performance and prevalence of PET or PET/CT.**

| Study, year | PET tracer | CIM Prior to PET | Prev | TP | FP | FN | TN |
|---|---|---|---|---|---|---|---|
| Ambrosini et al, 2012 [1] | $^{68}$Ga-DOTA-NOC | CT, MRI, US | 14.5% | 17 | 0 | 2 | 112 |
| Gabriel et al, 2007 [2] | $^{68}$Ga-DOTA-TOC | CT, Octreotide | 30.8% | 4 | 1 | 0 | 8 |
| Haidar et al, 2017 [3] | $^{68}$Ga-DOTA-NOC | NA | 27.4% | 31 | 3 | 3 | 87 |
| Haug et al, 2012 [4] | $^{68}$Ga-DOTA-TATE | CT, MRI, US | 34.6% | 29 | 7 | 7 | 61 |
| Sharma et al, 2014 [5]* | $^{68}$Ga-DOTA-NOC | CT, $^{131}$I-MIBG | 67.7% | 38 | 3 | 4 | 17 |
| Sharma et al, 2014 [6] | $^{68}$Ga-DOTA-NOC | CT, MRI, US, EUS, $^{131}$I-MIBG | 59.1% | 92 | 9 | 5 | 58 |

**Abbreviations:** CIM, conventional imaging; CT, computed tomography; EUS, endoscopic ultrasound; FN, false-negative; FP, false-positive; $^{131}$I-MIBG, $^{131}$I-metaiodobenzylguanidine scintigraphy, MRI, magnetic resonance imaging; NA, not available; PET, positron emission tomography; Prev, prevalence; TN, true-negative; TP, true-positive; US, ultrasonography
*Included only patients with suspicion of pheochromocytoma

**Figure 3-1: Forest plot of the sensitivity of PET or PET/CT in the diagnosis of suspected NETs.**

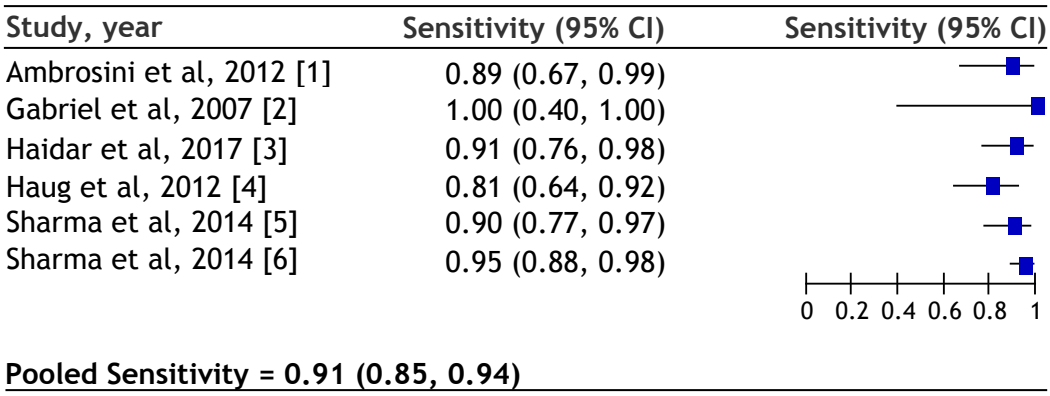
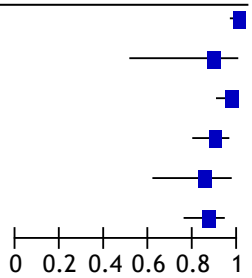


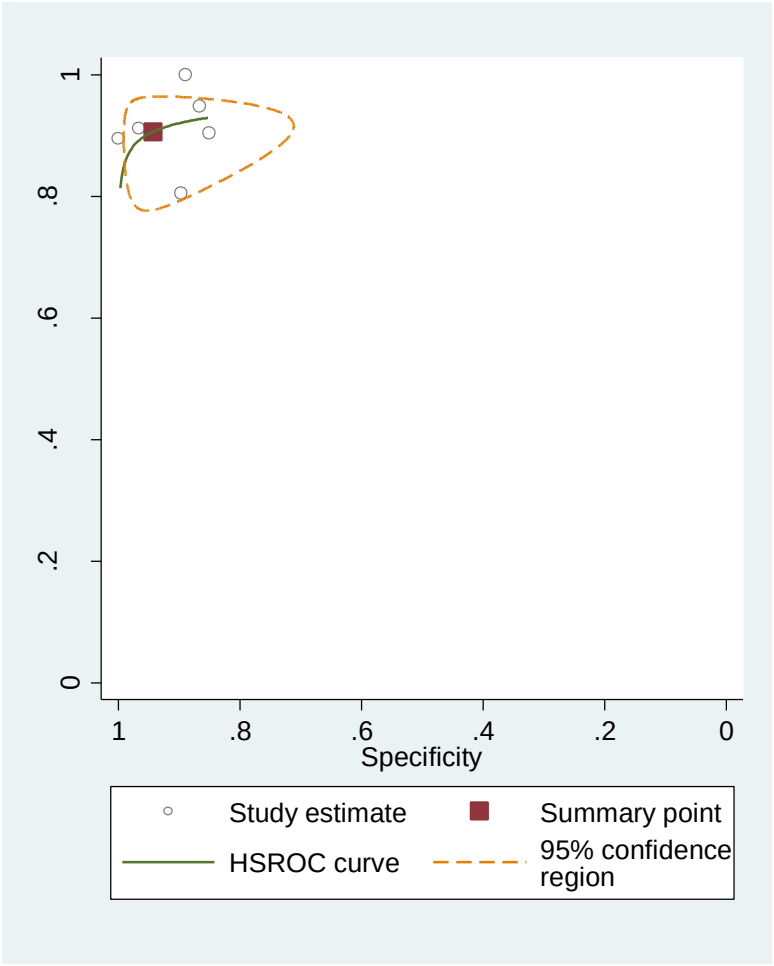
**Figure 3-2: Forest plot of the specificity of PET or PET/CT in the diagnosis of suspected NETs.**

| Study, year | Specificity (95% CI) | Specificity (95% CI) |
|---|---|---|
| Ambrosini et al, 2012 [1] | 1.00 (0.97, 1.00) | |
| Gabriel et al, 2007 [2] | 0.89 (0.52, 1.00) | |
| Haidar et al, 2017 [3] | 0.97 (0.91, 0.99) | |
| Haug et al, 2012 [4] | 0.90 (0.80, 0.96) | |
| Sharma et al, 2014 [5] | 0.85 (0.62, 0.97) | |
| Sharma et al, 2014 [6] | 0.87 (0.76, 0.94) | |




**Pooled Specificity = 0.94 (0.86, 0.98)**

**Figure 3-3: Summary receiver operating characteristic curve for the diagnostic performance of PET or PET/CT.**



***Staging and Restaging***

The evidence comparing the diagnostic accuracy of PET or PET/CT with conventional imaging in the setting of staging and restaging came from 14 studies (Table 3-3). Conventional imaging included octreotide, contrast-enhanced CT (CeCT)/CT, MRI, US, and bone scan. Among these studies, seven were of a prospective design [2,7-12] and seven were retrospective in nature [3,13-15,17,20,21]. Patients with various primary tumour sites were included in all of the studies [2,3,7,8,10-15,17,20,21], except for one study with only medullary thyroid carcinoma patients [9]. Direct comparison of PET or PET/CT with conventional imaging was reported in 10 studies [2,7-15], while four were single-arm PET/CT studies [3,17,20,21]. In the 10 direct-comparison studies, the sensitivity of PET or PET/CT for detecting primary and/or metastatic lesions ranged from 78.3% to 100%, whereas the specificity ranged from 50% to 100% [2,7-15]. When excluding the study that evaluated only patients with medullary thyroid carcinoma, the specificity improved to a range from 83% to 100% [2,7,8,10-15]. In contrast, the sensitivity of octreotide ranged from 42.4% to 98% and the specificity ranged from 93% to 100% [2,7-9,12,13]. For CeCT/CT, the sensitivity ranged from 47% to 100% and the specificity ranged from 33.3% to 98% [2,10,14,15]. As for MRI, the sensitivity ranged from 72% to 97.6% and specificity ranged from 90% to 100 % [8,10]. Among the four single-arm studies, Haidar et al [3] reported $^{68}$Ga-DOTA-NOC PET/CT sensitivity and specificity of 84.4% and 100%, respectively for staging, and 90.5% and 100%, respectively for follow-up. Sharma et al [21] also reported $^{68}$Ga-DOTA-NOC PET/CT sensitivity and specificity of 98.6% and 100%, respectively. Haug et al [17] reported $^{68}$Ga-DOTA-TATE PET/CT sensitivity and specificity of 89.7% and 82.4%, respectively. As well, Skoura et al [20] reported $^{68}$Ga-DOTA-TATE PET/CT sensitivity and specificity of 97% and 95.1%, respectively.

It is worthwhile to note that in two studies [11,14], separate diagnostic measures were reported for detecting primary tumour and the different sites of metastasis. Naswa et al [11] demonstrated that $^{68}$Ga-DOTA-NOC PET/CT was better than conventional imaging (CeCT, MRI, US) in detecting both the primary tumour (sensitivity, 78.3% versus 63.8%, $p<0.001$) and metastases (sensitivity, 97.4% versus 81.8%, $p<0.001$). On the other hand, the specificities were identical between the two imaging modalities. Similarly, Albanus et al [14] reported higher sensitivity (100% versus 47%, $p=0.0039$) and specificity (89% versus 49%, $p=0.0004$) for $^{68}$Ga-DOTA-TATE PET/CT in comparison to CeCT for detecting bone metastases. $^{68}$Ga-DOTA-TATE PET/CT was also more sensitive (92% versus 64%, $p=0.0156$) and more specific (83% versus 59%, $p=0.0386$) than CeCT when detecting lymph node metastases. For the detection of pulmonary metastases, the sensitivity (100% for both) was equal between $^{68}$Ga-DOTA-NOC PET/CT and CeCT, but specificity was higher for $^{68}$Ga-DOTA-NOC PET/CT (95% versus 82%, $p=0.0313$).

**Table 3-3: Diagnostic performance of PET or PET/CT versus conventional imaging in the detection of primary and metastatic lesions in patients with proven NETs or suspected recurrence.**

| Study, year | Indication** | Unit of analysis | Imaging modality | Sens | Spec | PPV % | NPV | Accu |
|---|---|---|---|---|---|---|---|---|
| ***Prospective*** | | | | | | | | |
| Gabriel et al, 2007 [2] | Staging (36) | Patient | $^{68}$Ga-DOTA-TOC PET | 97 | 100 | 100 | 75 | 97.2 |
| | | | Octreotide | 42.4 | 100 | 100 | 15.8 | 47.2 |
| | | | CT | 51.6 | 60 | 88.9 | 16.7 | 52.8 |
| | Follow-up (35) | Patient | $^{68}$Ga-DOTA-TOC PET | 97.1 | 100 | 100 | 50 | 97.1 |
| | | | Octreotide | 61.8 | 100 | 100 | 7.1 | 62.9 |
| | | | CT | 68.8 | 33.3 | 91.7 | 9.1 | 65.7 |
| Deppen et al, 2016 [7] | Staging (78) | Patient | $^{68}$Ga-DOTA-TATE PET/CT | 96* | 93 | 96 | 93 | 94* |
| | | | Octreotide | 72* | 93 | 95 | 65 | 82* |
| Etchebehere et al, 2014 [8] | Restaging (19) | Lesion | $^{68}$Ga-DOTA-TATE PET/CT | 96 | 97 | 94 | 98 | 97 |
| | | | Octreotide | 60 | 99 | 96 | 83 | 86 |
| | | | MRI | 72 | 100 | 100 | 88 | 91 |
| Yamaga et al, 2017 [9]*** | Restaging (15) | Patient | $^{68}$Ga-DOTA-TATE PET/CT | 100 | 50 | 92.9 | 100 | 93.3 |
| | | | Octreotide | 46.2 | 100 | 100 | 22.2 | 53.3 |
| | | | CT/MRI/US/bone scan | 100 | 50 | 92.9 | 100 | 93.3 |
| Schraml et al, 2013 [10] | Staging (51) | Patient | $^{68}$Ga-DOTA-TOC PET/CT | 97.6 | 100 | 100 | 90.9 | 98 |
| | | | CT | 90.2 | 90 | 97.4 | 69.2 | 90.2 |
| | | | MRI | 97.6 | 90 | 97.6 | 90 | 96.1 |
| Naswa et al, 2011 [11] | Staging (60), Restaging (49) | Patient | $^{68}$Ga-DOTA-NOC PET/CT$^{\dagger}$ | 78.3* | 92.5 | 94.7 | 71.1 | 83.5 |
| | | | CeCT/MRI/US$^{\dagger}$ | 63.8* | 92.5 | 93.6 | 59.7 | 74.3 |
| | | | $^{68}$Ga-DOTA-NOC PET/CT$^{\ddagger}$ | 97.4* | 100 | 100 | 94.1 | 98.2 |
| | | | CeCT/MRI/US$^{\ddagger}$ | 81.8* | 100 | 100 | 69.6 | 87.2 |
| Van Binnebeek et al, 2016 [12] | Therapy evaluation (53) | Lesion | $^{68}$Ga-DOTA-TOC PET/CT | 99.9* | NA | NA | NA | NA |
| | | | Octreotide | 60.1* | NA | NA | NA | NA |
| ***Retrospective*** | | | | | | | | |
| Haidar et al, 2017 [3] | Staging (193) | Patient | $^{68}$Ga-DOTA-NOC PET/CT | 84.4 | 100 | 100 | 61.1 | NA |
| | Follow-up (97) | Patient | $^{68}$Ga-DOTA-NOC PET/CT | 90.5 | 100 | 100 | 77.8 | NA |
| Srirajaskanthan et al, 2010 [13] | Equivocal CIM findings (51) | Patient | $^{68}$Ga-DOTA-TATE PET/CT | 87.2 | 100 | NA | NA | NA |
| | | | Octreotide | 98.0 | NA | NA | NA | NA |
| Sharma et al, 2015 [21] | Restaging (90) | Study | $^{68}$Ga-DOTA-NOC PET/CT | 98.6 | 100 | 100 | 93.3 | 98.8 |
| Haug et al, 2014 [17] | Restaging (33), Follow-up (30) | Patient | $^{68}$Ga-DOTA-TATE PET/CT | 89.7 | 82.4 | 81.3 | 90.3 | 85.7 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Albanus et al, 2015 [14] | Staging (27), Restaging (14), Follow-up (11), Therapy evaluation (2) | Patient | $^{68}$Ga-DOTA-TATE PET/CT[¶] | 100* | 89* | 81 | 100 | NA |
| | | | CeCT[¶] | 47* | 49* | 30 | 67 | NA |
| | | | $^{68}$Ga-DOTA-TATE PET/CT[μ] | 92* | 83* | 82 | 92 | NA |
| | | | CeCT[μ] | 64* | 59* | 57 | 65 | NA |
| | | | $^{68}$Ga-DOTA-TATE PET/CT [λ] | 100 | 95* | 83 | 100 | NA |
| | | | CeCT [λ] | 100 | 82* | 56 | 100 | NA |
| Ambrosini et al, 2010 [15] | Staging (49), UP (24), Restaging (33), Equivocal CIM findings (65), Follow-up (40), Therapy evaluation (12) | Patient | $^{68}$Ga-DOTA-NOC PET/CT | 100* | 100 | 100 | 100 | NA |
| | | | CT | 80* | 98 | 92 | 95 | NA |
| Skoura et al, 2016 [20] | Staging (294), Restaging (495), follow-up (307), UP (159), Equivocal CIM findings (3) | Study | $^{68}$Ga-DOTA-TATE PET/CT | 97 | 95.1 | 98.5 | 90.4 | 96.6 |

**Abbreviations:** Accu, accuracy; CIM, conventional imaging; CeCT, contrast-enhanced computed tomography; CT, computed tomography; MRI, magnetic resonance imaging; NA, not available; NET, neuroendocrine tumour; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; US, ultrasonography

*** Included only patients with medullary thyroid carcinoma

**Data in parentheses denotes the number of patients [2,3,7-15,17,21] or scans [20] referred for the indication.

*$p<0.05$ indicates significant differences between the values obtained by PET or PET/CT and other imaging modalities

[†]Diagnostic measures for detecting primary tumour.

[‡]Diagnostic measures for detecting metastases.

[¶]Diagnostic measures for detecting bone metastases.

[μ]Diagnostic measures for detecting lymph node metastases.

[λ]Diagnostic measures for detecting pulmonary metastases.

***Impact on Patient Management***

Nine studies evaluated the impact of PET/CT on patient management (Table 3-4). $^{68}$Ga-DOTA-TATE was used in five studies [7,13,16,17,20], $^{68}$Ga-DOTA-NOC in two studies [11,18], and $^{68}$Ga-DOTA-TOC in two studies [10,19]. Furthermore, four studies [7,10,16,17] reported change in intended management after PET/CT, whereas management change was implemented in five studies [11,13,18-20]. Overall, change in management occurred in 45% (95% CI, 36% to 55%) of cases, with the majority of the changes involving surgical planning and patient selection for peptide receptor radionuclide therapy (PRRT) (Figure 3-4). All treatment changes as a consequence of PET/CT are listed in Table 3-5.

**Table 3-4: Characteristics of studies reporting change in patient management.**

| Study, year | PET tracer | CIM Prior to PET | Management Change |
|---|---|---|---|
| Deppen et al, 2016 [7] | $^{68}$Ga-DOTA-TATE | CT, MRI, Octreotide | Intended |
| Schraml et al, 2013 [10] | $^{68}$Ga-DOTA-TOC | MRI | Intended |
| Herrmann et al, 2015 [16] | $^{68}$Ga-DOTA-TATE | NA | Intended |
| Haug et al, 2014 [17] | $^{68}$Ga-DOTA-TATE | NA | Intended |
| Srirajaskanthan et al, 2010 [13] | $^{68}$Ga-DOTA-TATE | CT, MRI, Octreotide | Implemented |
| Ambrosini et al, 2010 [18] | $^{68}$Ga-DOTA-NOC | CT, MRI | Implemented |
| Frilling et al, 2010 [19] | $^{68}$Ga-DOTA-TOC | CT, MRI | Implemented |
| Naswa et al, 2011 [11] | $^{68}$Ga-DOTA-NOC | CeCT, MRI, US | Implemented |
| Skoura et al, 2016 [20] | $^{68}$Ga-DOTA-TATE | NA | Implemented |

**Abbreviations:** CIM, conventional imaging; CT, computed tomography; MRI, magnetic resonance imaging; NA, not available; PET, positron emission tomography; US, ultrasonography

**Figure 3-4: Forest plot of the overall impact of PET/CT on clinical management.**

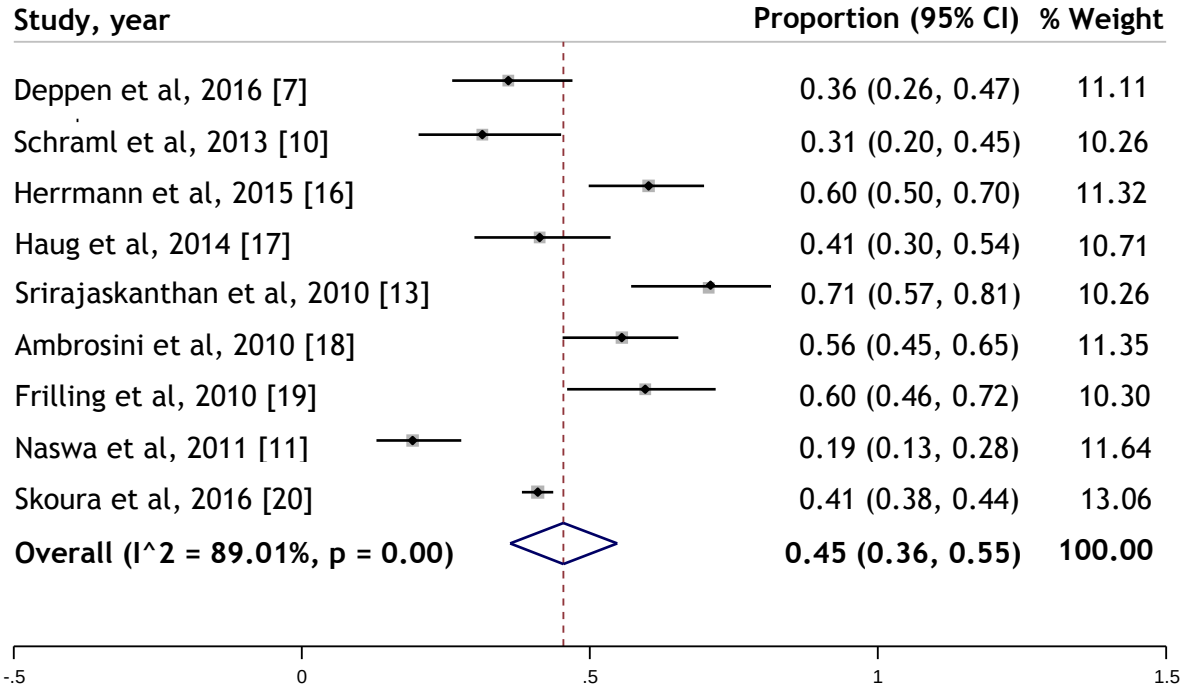


**Table 3-5: Modification of treatment plan after PET/CT.**

| Study, year | n* | Modification details |
|---|---|---|
| Deppen et al, 2016 [7] | 28 | 12: referred for PRRT<br>9: intramodality changes<br>7: surgery cancelled or a radical change in type of surgery |
| Schraml et al, 2013 [10] | 16 | 16: provided relevant information for deciding to use PRRT |
| Herrmann et al, 2015 [16] | 53 | 20: switched to treatment without chemotherapy<br>6: changed from watch-and-wait to other treatment strategies<br>5: switched to watch-and-wait<br>3: added chemotherapy<br>3: changed from surgery to surgery + octreotide or watch-and-wait<br>1: changed from a multimodality approach to surgery alone<br>15: others** |
| Haug et al, 2014 [17] | 26 | 11: considered for surgery<br>6: initiated chemotherapy<br>5: commenced radioactively labeled somatostatin analogs<br>3: commenced somatostatin analogues<br>1: local treatment of liver metastases |
| Srirajaskanthan et al, 2010 [13] | 36 | 20: referred for PRRT<br>7: commenced somatostatin analogues<br>4: excluded from PRRT<br>4: considered for surgery<br>1: switched to watch-and-wait |
| Ambrosini et al, 2010 [18] | 50 | 25: referred for PRRT<br>6: surgery cancelled<br>5: considered for surgery<br>4: continued somatostatin analogues<br>3: commenced somatostatin analogues<br>2: excluded from somatostatin analogues<br>1: continued PRRT<br>1: initiated radiotherapy<br>1: indicated for further diagnostic procedure<br>1: eligible for liver transplant<br>1: received combined PRRT and surgery |
| Frilling et al, 2010 [19] | 31 | 17: change in non-surgical treatment<br>14: change in surgical strategy |
| Naswa et al, 2011 [11] | 21 | 8: considered for surgery<br>6: change in surgical planning<br>4: surgery cancelled<br>2: change in treatment regimen<br>1: ruled out liver metastases |
| Skoura et al, 2016 [20] | 515 | 362: initiated chemotherapy or PRRT<br>71: additional chemotherapy<br>52: considered for surgery |

5: excluded suspected NETs
2: stopped previous treatment
2: excluded from PRRT
2: eligible for liver transplant
19: unclear‡

**Abbreviations:** CT, computed tomography; NETs, neuroendocrine tumours; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy
*n denotes reported management change in the number of patients [7,10,11,13,17-19] or scans [20].
**Includes other intermodality or intramodality changes.
‡Precise management change was unclear from the records.

***Treatment Response***

One study evaluated $^{68}$Ga-DOTA-TOC PET for assessing response to PRRT. Forty-six patients with advanced NETs were investigated before and after two to seven cycles of $^{90}$Y-DOTA-TOC or $^{177}$Lu-DOTA-TATE. According to visual response criteria, $^{68}$Ga-DOTA-TOC PET showed no advantage over CT for assessing response to therapy (accuracy, 91.3% versus 78.3%, respectively, p=0.27) [22].

***Routine Surveillance***

There were no studies identified that met the study selection criteria examining PET or PET/CT in the routine surveillance of NETs.

***Ongoing, Unpublished, or Incomplete Studies***

The National Cancer Institute of Clinical Trials Database (https://www.clinicaltrials.gov/) was searched on November 2, 2017 for potential trials meeting the selection criteria for this systematic review. There was one ongoing trial identified that would be eligible for inclusion in the update of this recommendation report in the future.

| **Safety & Efficacy of $^{68}$Ga-DOTA-tyr3-Octreotide PET/CT in Diagnosis, Staging & Measurement of Response to Treatment in Patients With Somatostatin Receptor Positive Tumors: Comparison to Octreoscan Plus High-Resolution, Contrast Enhanced CT.** | |
|---|---|
| **Protocol ID:** | NCT01619865 |
| **Study type:** | Interventional |
| **Estimated enrollment:** | 200 |
| **Last updated:** | April 30, 2017 |
| **Estimated study completion date:** | December 2018 |
| **Sponsor:** | University of Iowa |
| **Status:** | Ongoing, but not recruiting participants |

**DISCUSSION**

NETs are an uncommon but incredibly diverse group of malignancies. The considerable heterogeneity of this disease makes classification as well as clinical characterization and staging extremely important factors in determining the best possible treatment in a person-centred fashion. Staging, anatomical site of origin, and somatostatin receptor status can have profound impact on treatment choices for patients and thus must be effectively and appropriately characterized in most neuroendocrine patients. Functional imaging plays a

pivotal role in the care of NETs due to the potential presence of somatostatin receptors. Conventional cross-sectional imaging (CT/MRI) remains the foundation for imaging in NETs, much like in other cancers. Functional imaging not only add valuable supplemental information to conventional cross-sectional imaging but can also help quantify somatostatin receptor status and assess for appropriate treatments such as PRRT. A recent phase 3 randomized clinical trial published in the *New England Journal of Medicine* [43] has shown significant efficacy for $^{117}$Lu-Dotatate in gastrointestinal NETs and the use of this treatment is expected to grow exponentially in the coming years. Functional imaging plays a crucial role in the decision to initiate this treatment.

Currently, octreoscan is the predominantly used functional imaging modality in Ontario; however, there is a lack of uniform availability for this modality in the province. With the emergence of $^{68}$Ga PET as a promising functional imaging modality, there is a need to evaluate its efficacy, availability, and appropriate use. While it is widely recognized that $^{68}$Ga PET is superior to octreoscan for most indications in NETs, it is important to establish evidence-based recommendations for the use of $^{68}$Ga PET that would allow for optimal patient-centred care and feasible access to this modality in Ontario. Generally, the data supporting the use of $^{68}$Ga PET are incomplete and limited. The studies published to date are often small in number with many lacking a control arm. Owing to the varied endpoints being evaluated, there is a great degree of heterogeneity. This is evident from the presence of a significant $I^2$ statistic (89.0%, p=0.00) in the overall impact of PET/CT on clinical management, where the definition of "change management" differed from study to study. Furthermore, most studies consisted of a mixed population of NETs patients, which makes developing recommendations and generalizations problematic. Given these challenges, the Working Group considered advocating for the use of $^{68}$Ga PET where there is evidence showing improvement in diagnostic outcomes and conditions where the use of $^{68}$Ga PET had the potential to change management. The evidence generally fell within the areas of 1) initial diagnosis where $^{68}$Ga PET would aid with diagnosis when more conventional testing remained equivocal; 2) pre-operative staging to help plan surgical extent and determine which patients are best suited for surgical resection; 3) to determine the suitability of PRRT therapy based on the identification of somatostatin receptors; and 4) restaging of patients with evidence of clinical and/or biochemical progression. Conversely, the Working Group members felt strongly that there is insufficient evidence to recommend the use of $^{68}$Ga PET in the assessment of treatment response or in the routine surveillance of NETs. As new data become available in the future, this would be re-examined but currently there does not appear to be a demonstrable benefit for patients to undergo $^{68}$Ga PET in these circumstances. Acknowledging the limitations in the literature, this presents an opportunity for the partnership of CCO, the clinical community, and the patient community to collect higher-quality evidence to help evaluate the best uses of $^{68}$Ga PET in a cost-effective and person-centred fashion.

Recently, the FDA approved NETSPOT™ $^{68}$Ga DOTA-TATE imaging and a group of clinical experts in NETs conveyed a panel in conjunction with the Society of Nuclear Medicine to determine the appropriate use of $^{68}$Ga in NETs patients in the United States. This group reviewed the evidence for the imaging modality much like our Working Group but generally based their recommendations on very specific clinical scenarios. The approach of our Working Group was to consider more general principles for the use of $^{68}$Ga PET rather than restrictive clinical scenarios as we believed this allowed for greater flexibility and a more patient-centred delivery of the treatment. Despite the different approach taken, there was a high level of overall agreement between the recommendations. However, the Working Group did not find sufficient evidence to support the AUC recommendations in the use of $^{68}$Ga PET for monitoring treatment response or routine follow-up [33].

**CONCLUSIONS**

$^{68}$Ga PET is recommended for initial diagnosis where conventional testing remained equivocal, for staging of patients with localized primary and/or limited metastasis where definitive surgery is planned, to determine somatostatin receptor status and suitability for PRRT, and for staging of patients where detection of occult disease will alter the treatment options and decision making. There is insufficient evidence at this time to recommend the use of $^{68}$Ga PET as part of treatment response assessment and routine follow-up.

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**Appendix 1: Members of the Working Group and their COI declaration**

| Name | Affiliation | Declarations of interest |
|---|---|---|
| **Simron Singh, MD, MPH, FRCPC**<br>Medical Oncologist | Department of Medicine, Medical Oncology and Hematology, University of Toronto and Odette Cancer Research Program, Sunnybrook Research Institute | No conflict declared |
| **Raymond Poon, MPH**<br>Health Research Methodologist | Department of Oncology, McMaster University, Juravinski Hospital Site | No conflict declared |
| **Rebecca Wong, MSc, MD, FRCPC**<br>Radiation Oncologist | Department of Radiation Oncology, University of Toronto and Princess Margaret Hospital, University Health Network | No conflict declared |
| **Ur Metser, MD, FRCPC**<br>Radiologist | Joint Department of Medical Imaging, University Health Network, Mount Sinai Hospital and Women's College Hospital, University of Toronto | No conflict declared |

**Appendix 2: Literature Search Strategy**

The search was conducted in MEDLINE (1946 to May Week 2 2017), EMBASE (1974 to 2017 Week 19), and Cochrane Database of Systematic Reviews (2005 to May 9, 2017) on May 09, 2017.

**MEDLINE**

| | | |
|---|---|---|
| **Section A: Disease and/or population** | 1 | exp Neuroendocrine Tumors/ |
| | 2 | (neuroendocrine adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp. |
| | 3 | exp Carcinoid Tumor/ |
| | 4 | (insulinoma or gastrinoma$ or glucagonoma$ or vasoactive intestinal peptideoma$ or VIPoma$).mp. |
| | 5 | (PPoma$ or somatostatinoma$ or ACTHoma$ or parathyroid hormone-related peptide tumo?r$ or PTHrp secreting tumo?r$).mp. |
| | 6 | ((pancreatic adj1 endocrine tumo?r$) or pancreatic islet cell tumo?r$ or GEP-Net$ or NE-GEP$ or NET$).mp. |
| | 7 | (Multiple endocrine neoplasia$ or (neuroblastoma$ or ph?eochromocytoma$ or paraganglioma$)).mp. |
| | 8 | (appendiceal endocrine adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 9 | (goblet cell adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 10 | (merkel cell adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 11 | (medullary adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 12 | or/1-11 |
| **Section B: Intervention or diagnostic test** | 13 | Exp Gallium Radioisotopes/ or dota?tate.mp. or dota?noc.mp. or dota?toc.mp. or dota$.mp. or 68?ga$.mp. or ga?68$.mp. or 68?gallium$.mp. or gallium?68$.mp. |
| | 14 | (positron emission tomography computed tomography or pet ct or pet?ct).mp. |
| | 15 | exp Tomography, Emission-computed/ |
| | 16 | exp positron emission tomography/ |
| | 17 | (positron adj emission adj tomograph$).mp. |
| | 18 | (pet$ or pet scan$).mp. |
| | 19 | or/15-18 |

| | | |
|---|---|---|
| | 20 | 13 and (14 or 19) |
| **Section C: Exclusion strategy** | 21 | (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. |
| | 22 | animal/ not (exp human/ or humans/) |
| | 23 | 21 or 22 |
| **Combining Sections A, B, and C** | 24 | (12 and 20) not 23 |
| | 25 | limit 24 to English language |

**EMBASE**

| | | |
|---|---|---|
| **Section A: Disease and/or population** | 1 | exp Neuroendocrine Tumors/ |
| | 2 | (neuroendocrine adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp. |
| | 3 | exp Carcinoid Tumor/ |
| | 4 | (insulinoma or gastrinoma$ or glucagonoma$ or vasoactive intestinal peptideoma$ or VIPoma$).mp. |
| | 5 | (PPoma$ or somatostatinoma$ or ACTHoma$ or parathyroid hormone-related peptide tumo?r$ or PTHrp secreting tumo?r$).mp. |
| | 6 | ((pancreatic adj1 endocrine tumo?r$) or pancreatic islet cell tumo?r$ or GEP-Net$ or NE-GEP$ or NET$).mp. |
| | 7 | (Multiple endocrine neoplasia$ or (neuroblastoma$ or ph?eochromocytoma$ or paraganglioma$)).mp. |
| | 8 | (appendiceal endocrine adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 9 | (goblet cell adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 10 | (merkel cell adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 11 | (medullary adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 12 | or/1-11 |
| **Section B: Intervention or diagnostic test** | 13 | Exp Gallium Radioisotopes/ or dota?tate.mp. or dota?noc.mp. or dota?toc.mp. or dota$.mp. or 68?ga$.mp. or ga?68$.mp. or 68?gallium$.mp. or gallium?68$.mp. |

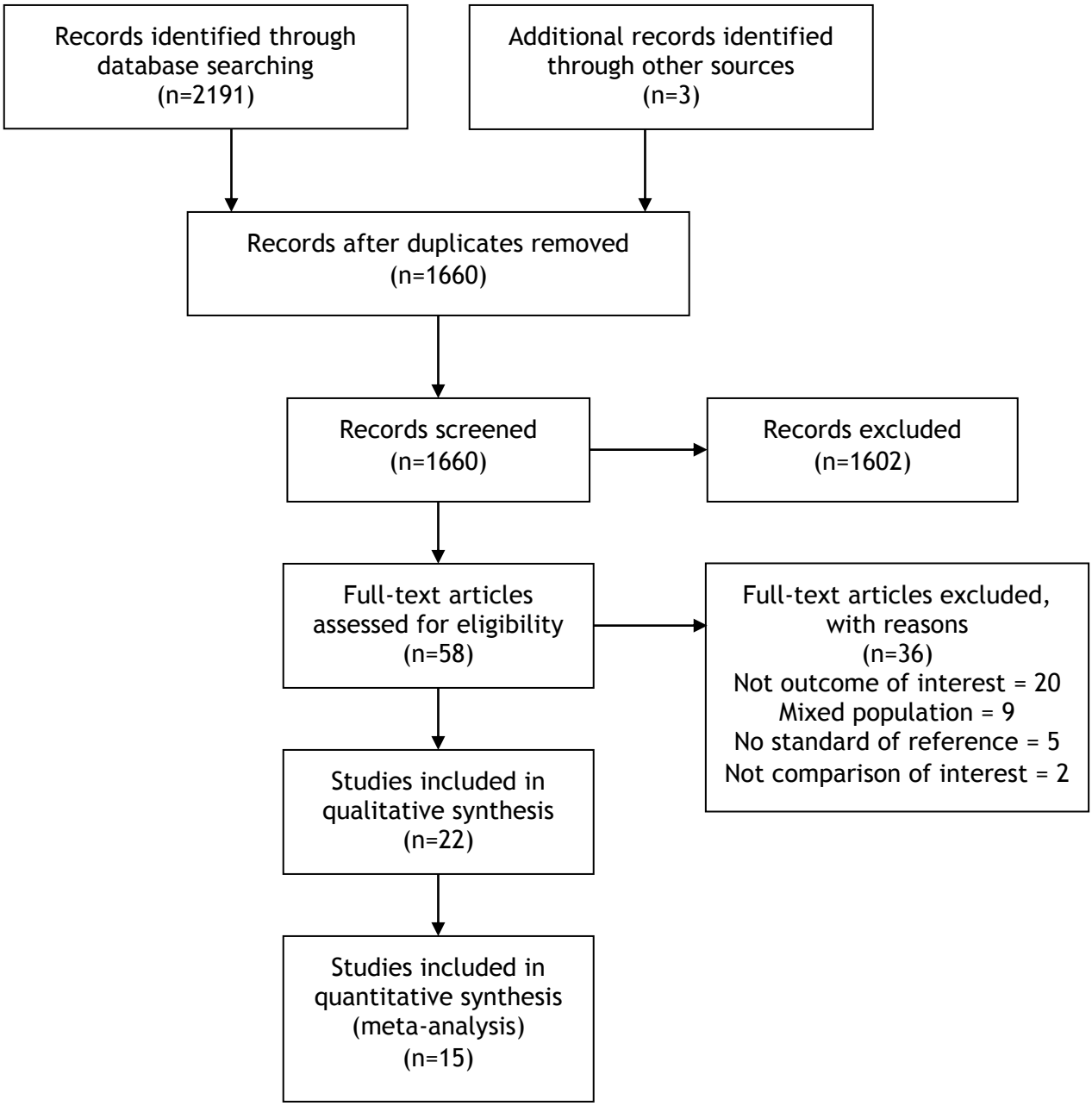
| | | |
|---|---|---|
| | 14 | (positron emission tomography computed tomography or pet ct or pet?ct).mp. |
| | 15 | exp Tomography, Emission-computed/ |
| | 16 | exp positron emission tomography/ |
| | 17 | (positron adj emission adj tomograph$).mp. |
| | 18 | (pet$ or pet scan$).mp. |
| | 19 | or/15-18 |
| | 20 | 13 and (14 or 19) |
| **Section C: Exclusion strategy** | 21 | (editorial or note or letter erratum or short survey).pt. or letter/ or case study/ |
| | 22 | animal/ not (exp human/ or humans/) |
| | 23 | 21 or 22 |
| **Combining Sections A, B, and C** | 24 | (12 and 20) not 23 |
| | 25 | limit 24 to English language |

**Cochrane Database of Systematic Reviews**

| | | |
|---|---|---|
| **Section A: Disease and/or population** | 1 | (neuroendocrine adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp. |
| | 2 | (insulinoma or gastrinoma$ or glucagonoma$ or vasoactive intestinal peptideoma$ or VIPoma$).mp. |
| | 3 | (PPoma$ or somatostatinoma$ or ACTHoma$ or parathyroid hormone-related peptide tumo?r$ or PTHrp secreting tumo?r$).mp. |
| | 4 | ((pancreatic adj1 endocrine tumo?r$) or pancreatic islet cell tumo?r$ or GEP-Net$ or NE-GEP$ or NET$).mp. |
| | 5 | (Multiple endocrine neoplasia$ or (neuroblastoma$ or ph?eochromocytoma$ or paraganglioma$)).mp. |
| | 6 | (appendiceal endocrine adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 7 | (goblet cell adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 8 | (merkel cell adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |

| | | |
|---|---|---|
| | 9 | (medullary adj (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or maligan$ or tumo?r$)).mp. |
| | 10 | or/1-9 |
| **Section B: Intervention or diagnostic test** | 11 | dota?tate.mp. or dota?noc.mp. or dota?toc.mp. or dota$.mp. or 68?ga$.mp. or ga?68$.mp. or 68?gallium$.mp. or gallium?68$.mp. |
| | 12 | (positron emission tomography computed tomography or pet ct or pet?ct).mp. |
| | 13 | (positron adj emission adj tomograph$).mp. |
| | 14 | (pet$ or pet scan$).mp. |
| | 15 | or/12-14 |
| | 16 | 11 and 15 |
| **Combining Sections A and B** | 17 | 10 and 16 |

**Appendix 3: PRISMA Flow Diagram**



**Appendix 4: QUADAS-2 Assessment of Study Quality**

| Study | RISK OF BIAS | | | | APPLICABILITY CONCERNS | | |
|---|---|---|---|---|---|---|---|
| | PATIENT SELECTION | INDEX TEST | REFERENCE STANDARD | FLOW AND TIMING | PATIENT SELECTION | INDEX TEST | REFERENCE STANDARD |
| **Diagnosis/Staging/Restaging** | | | | | | | |
| Gabriel et al, 2007 [2] | L | L | L | L | L | L | L |
| Haidar et al, 2017 [3] | L | U | U | L | L | L | L |
| **Diagnosis** | | | | | | | |
| Ambrosini et al, 2012 [1] | L | U | U | L | L | L | L |
| Haug et al, 2012 [4] | L | U | U | L | L | L | L |
| Sharma et al, 2014 [5] | L | U | U | L | L | L | L |
| Sharma et al, 2014 [6] | L | U | U | L | L | L | L |
| **Staging/Restaging** | | | | | | | |
| Deppen et al, 2016 [7] | L | L | L | L | L | L | L |
| Etchebehere et al, 2014 [8] | L | L | U | L | L | L | L |
| Yamaga et al, 2017 [9] | L | L | U | L | L | L | L |
| Schraml et al, 2013 [10] | L | L | U | L | L | L | L |
| Naswa et al, 2011 [11] | L | L | U | L | L | L | L |
| Van Binnebeck et al, 2016 [12] | L | L | U | L | L | L | L |
| Srirajaskanthan et al, 2010 [13] | L | U | U | L | L | L | L |
| Albanus et al, 2015 [14] | L | L | U | L | L | L | L |
| Ambrosini et al, 2010 [15] | L | L | U | L | L | L | L |
| Herrmann et al, 2015 [16] | L | L | L | L | L | L | L |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Haug et al, 2014 [17] | H | U | U | L | L | L | L |
| Ambrosini et al, 2010 [18] | L | U | U | L | L | L | L |
| Frilling et al, 2010 [19] | L | L | U | L | L | L | L |
| Skoura et al, 2016 [20] | L | U | U | L | L | L | L |
| Sharma et al, 2015 [21] | L | U | U | L | L | L | L |
| **Treatment Response** | | | | | | | |
| Gabriel et al, 2009 [22] | L | L | L | L | L | L | L |

L=Low Risk H=High Risk U=Unclear Risk