$^{68}$Ga-DOTATOC Imaging of Neuroendocrine Tumors:

A Systematic Review and Meta-Analysis

Michael M. Graham$^1$, Xiaomei Gu$^2$, Timothy Ginader$^3$, Patrick Breheny$^3$, John J. Sunderland$^1$

1. Department of Radiology, Division of Nuclear Medicine, University of Iowa, Iowa City, IA, USA

2. Hardin Library for the Health Sciences, University of Iowa, Iowa City, IA, USA

3. Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA

First and corresponding author:

Michael M. Graham, PhD, MD

Division of Nuclear Medicine

Department of Radiology, Room 3863 JPP

University of Iowa Hospitals and Clinics

200 Hawkins Drive

Iowa City, IA 52242 USA

Tel: (319) 356-3380; Fax (319) 356-2220; michael-graham@uiowa.edu

Word count: 4577

Acknowledgment: Marin L. Schweizer, for helping design the meta-analysis approach.

Running foot line: $^{68}$Ga-DOTATOC Imaging of NETs
ABSTRACT

$^{68}$Ga-DOTATOC, a somatostatin receptor targeted ligand, has been used clinically in Europe over the past decade for imaging neuroendocrine tumors (NETs). It appears to be quite sensitive and effective for clinical management decision-making. This meta-analysis summarizes the efficacy of $^{68}$Ga-DOTATOC for several distinct indications and is intended to support approval of this agent by the U.S. Food and Drug Administration.

Methods The major electronic medical databases were searched for relevant papers over the period from January 2001 until November 2015. Papers were selected for review in 3 categories: clinical trials that reported sensitivity and specificity, comparison studies with $^{111}$In-octreotide, and change of management studies. All the eligible papers underwent Quality Assessment of Diagnostic Accuracy Studies (QUADAS) assessment, which was useful in the final selection of papers for review.

Results The initial search yielded 468 papers. After detailed evaluation, 17 papers were finally selected. Five types of studies emerged: workup of patients with symptoms and biomarker findings suggestive of NET, but with negative conventional imaging (3 papers, yield was only 13%); sensitivity (12 papers, sensitivity 92%,) and specificity (7 papers, specificity 82%); identification of site of unknown primary in patients with metastatic NET (4 papers, yield was 44%); impact on subsequent NET patient management (4 papers – change in management in 51%); and comparison with $^{111}$In-octreotide (2 papers, sensitivity of DOTATOC on a per lesion basis was 100%, for $^{111}$In-octreotide was 78.2%; specificity was not available). Safety was not explicitly addressed in any study, but there were no reports of adverse events.
Conclusion 68Ga-DOTATOC is useful for evaluating the presence and extent in disease for staging, restaging, and to assist in treatment decision making for patients with NET. It is also effective in locating the site of an unknown primary in NET patients that present with metastatic NET, but no known primary tumor. It also appears to be more accurate than 111In-octreotide. Although 68Ga-DOTATOC would seem to be useful in evaluating patients with suggestive symptoms and biomarker findings, it does not perform well in this setting and has low yield. Overall, it appears to be an excellent imaging agent to assess patients with known NET and frequently leads to a change in management.

Key Words: neuroendocrine; DOTATOC; octreotide; pentetreotide; systematic review; meta-analysis
Neuroendocrine tumors (NETs) are a class of slow-growing tumors that arise from cells distributed mainly in the lungs, gastrointestinal tract, or pancreas. NETs have been considered to be rare neoplasms, but an analysis from Surveillance, Epidemiology and End Results (SEER) reports a fivefold increase from 1973 (1.09/100,000) to 2004 (5.25/100,000) (1). This increase has been ascribed, in part, to improved methods of diagnosis and greater disease awareness. Overall 5-year survival is about 75% and is strongly dependent on stage and grade of the tumor (1). Surgery can be curative for early stage disease, but metastatic disease is often present at the time of presentation, precluding complete resection. Chemotherapy and hormonal blockade are effective in slowing progression, but are rarely curative.

A unique feature of NETs is their overexpression of somatostatin receptors on the tumor cells, which has established the basis for both diagnostic imaging, and peptide receptor radionuclide therapy. The first approved somatostatin receptor ligand for imaging neuroendocrine tumors was octreotide, labeled with In-111. The agent is an 8-peptide sequence linked to DTPA, which is a chelator that binds the In-111. The 8-peptide sequence is a subset of the amino acids in somatostatin, and has been demonstrated to avidly bind to the type 2 somatostatin receptor (2). The commercial radiopharmaceutical, Octreoscan, was approved on June 2, 1994.

Although In-111 octreotide has been successfully used in thousands of patients with NETs over the past two decades, it does have some limitations. Because of the relative high energy of the gamma rays from In-111 (171 keV and 245 keV) a medium energy collimator must be used and spatial resolution is degraded compared to Tc-99m agents. The localization of In-111 octreotide is relatively slow, so that imaging is usually done at 4 and 18 to 24 hours after injection.
Positron Emission Tomography (PET) has significantly higher spatial resolution than gamma camera imaging and in the late 1990s a new PET agent, $^{68}$Ga-DOTATOC was shown to rapidly localize to NETs and imaging could be accomplished at one hour after injection. The first paper on clinical imaging with $^{68}$Ga-DOTATOC was published in 2001(3). Over the following few years it began to be widely used in Europe including The Netherlands, Germany, Austria, Italy and several other countries to image NETs to assist in the identification of sites of disease and to help in the management of these patients. In recent years all imaging has been done with combined PET imaging with Computed Tomography (PET/CT).

Most of the published medical literature derives from sites in Europe, with a few more recent papers from India, Korea, Taiwan, and Japan. Because of the different regulatory systems in these countries, almost all use of $^{68}$Ga-DOTATOC has been in clinical management of NET patients and not in well controlled clinical trials. Accordingly, in most of the papers the reference standard is suboptimal or biased and no rigorous safety studies have been done. In spite of this, the results that have been reported are remarkably consistent and there is little question that this agent is safe, effective, and more accurate than In-111 octreotide, the standard for the past 22 years.
METHODS

Literature Search

A health sciences librarian performed literature searches in November 2015 for English language studies from 2000 to 2015. The start date of 2000 was chosen because the first paper on the use of Ga-68 DOTATOC in humans was published in 2001. Databases searched included MEDLINE/PubMed, Embase.com, the Cochrane Register of Diagnostic Test Accuracy Studies, and the Cochrane Central Register of Controlled Trials. In all databases, the following search strategy was used without any search field tags: (68Ga OR Ga68 OR Ga-68 OR Ga OR gallium) AND DOTATOC. There is not a subject term for Gallium-68 DOTATOC in either PubMed or Embase. One logical workaround would be utilizing phrase searching and proximity searching to supplement subject term searching. But a search strategy simply utilizing the Boolean operator <AND> works better in this case than other complex strategies, because DOTATOC is a very exact subject term. Similarly, it is not necessary to include terms for neuroendocrine tumors (NETS).

Study Selection

The studies identified from the literature search were evaluated for duplicates and were then categorized independently by two experts (MMG and JJS) into 13 categories (Fig 1). Many studies were not relevant for evaluation of clinical performance and were eliminated. After careful evaluation for relevance and quality, three categories of papers were identified that met all criteria. The three categories were: clinical trial studies with information relevant to sensitivity and specificity; studies comparing Ga-68 DOTATOC to In-111 octreotide; and change of management studies.
Data Abstraction

A data abstraction sheet was developed (Appendix 1). Two reviewers independently assessed the collected data. A consensus was reached after discussion with a third reviewer. The key information that was abstracted included: number of subjects, tumor type, reference standard, interpretation criteria, type of paper (see 5 groups of papers, below), and outcome, i.e. sensitivity, specificity, percent change in management, yield in finding an unknown primary.

Quality assessment of individual studies

A quality assessment sheet was developed based on QUADAS-2 (4) (Appendix 2). The quality elements determined for each paper were: adequacy of blinding, reference standard, patient selection criteria, study design, and description of image interpretation criteria. The overall quality of each paper was determined and was used in selecting the final papers for review. However, as recommended by the developers of QUADAS we did not use a threshold applied to the sum QUADAS score for determination of paper acceptability.

Data synthesis and statistical analysis

A bivariate normal random-effects model (5) for the joint meta-analysis of analyzing sensitivity and specificity was used to assess the effects of DOTATOC screening in the established literature. This method accounts for variation occurring between studies as well as the correlation between sensitivity and specificity. We also analyzed a measure of overall accuracy called the diagnostic odds ratio, defined as the ratio of the odds of a positive test for a diseased patient to the odds of a positive test for a non-diseased patient. The diagnostic odds
ratio (6), a function of both sensitivity and specificity, was used to provide a univariate measure of accuracy. The DerSimonian-Laird random effects model (7) was used to analyze diagnostic odds ratios on a log scale. Finally, change of management was calculated using a raw proportion of the number of patients whose management was changed divided by the total number of patients. The data were then analyzed on the log-odds scale to provide a normalizing transformation, with a Gaussian random effects model and Residual Maximum Likelihood (REML) estimation used to carry out the meta-analysis. All analyses were performed in R and all confidence intervals are at the 95% significance level. The “madauni” and “reitsma” commands of the “mada” package in R were used for the diagnostic odds ratio, and sensitivity/specificity estimates respectively. The “rma.uni” command of the “metafor” package was used for the change in management proportion. Figures were created using SAS v9.4 (SAS Institute, Cary, NC).
RESULTS

Study Selection

A total of 634 references were found with 227 from PubMed, 405 from EMBASE, and 2 from Cochrane. After the removal of duplicated references, a total of 468 were left. The details for selecting 17 suitable papers are detailed in Fig 1.

It was apparent from examination of the available published literature that there are several different indications or clinical settings where $^{68}$Ga-DOTATOC was likely to be useful. In the analysis below we have separated the papers into six different groups to address the different types of studies. These groups are described below and literature data attributed to each group are tabulated in Table 1:

1. Diagnosis of disease in patients with symptoms and blood chemistry strongly suggestive for NET, particularly carcinoid (3 papers).
2. Sensitivity and specificity of $^{68}$Ga-DOTATOC (12 papers).
3. Identification of the site of an unknown primary in patients with metastatic NET, typically in the liver (4 papers).
4. Determination of the impact of $^{68}$Ga-DOTATOC imaging on subsequent patient management in patients with known NET (4 papers).
5. Sensitivity and specificity of $^{68}$Ga-DOTATOC in comparison to $^{111}$In-octreotide (2 papers).
   In addition, it also became clear that the sensitivity of $^{68}$Ga-DOTATOC for detection of atypical carcinoid is much lower than for typical carcinoid tumors. Two papers explicitly looked at this characteristic and are reported separately.
The sensitivity and specificity and the unknown primary literature were considered robust enough for formal meta-analysis. All other categories were deemed to not have sufficient data to warrant a true-meta-analysis, so summary statistics are provided.

**Sensitivity and Specificity (Meta-Analysis)**

The results of the meta-analysis on the first seven papers (8-14), that reported true positive, true negative, false positive and false negative results (N=432) show an overall sensitivity and specificity (with 95% confidence intervals) of 92% (85%, 96%) and 82% (69%, 90%) respectively (Fig 2). The diagnostic odds ratio for these papers is 61 (Fig 3). When we include the five papers (15-19) that only reported true positive and false negative results (N=214), the meta-analysis resulted in an overall sensitivity of 93% (87%, 96%). See Table 2.

**Change of Management (Meta-Analysis)**

There were 4 eligible papers that reported change in management following ⁶⁸Ga-DOTATOC PET/CT imaging (13,15,20,21). All the studies were retrospective, based on chart review. All patients had histologically confirmed or suspected multiple neuroendocrine tumors. In the combined papers 188 patients were imaged with a reported change of management in 51% (39%, 62%) (Fig 4).

**Unknown Primary (Summary Statistics)**

There were four eligible papers (Table 3) that reported on performance of ⁶⁸Ga-DOTATOC PET/CT for detecting an unknown primary in patients with extensive metastatic disease (15,18,22,23). The overall success rate was 40 of 91 or 43.9%. 
Diagnosis in patients suspected to have NET (Summary Statistics)

There were 3 papers that reported results on $^{68}$Ga-DOTATOC imaging in patients with symptoms and elevated blood biomarkers strongly suggestive of NET, but with no evidence of disease with conventional imaging (8,18,22). The biomarkers included Chromogranin A, ACTH, Gastrin, Insulin, and 5-HIAA. All of the papers also included patients with other indications. Reference standard was histology or follow-up with conventional imaging. Negative studies were scored as true negative. Among the papers reviewed (Table 4), there were 57 patients studied with this indication with an overall yield of 7 true positives (12%) and one false positive.

Other types of papers

Comparison with Octreoscan and Typical and Atypical Carcinoids

These papers do not report true negative or false positive values, thus specificity and diagnostic odds ratio cannot be calculated. Furthermore, with just two studies appearing in the literature, there is insufficient data to carry out a reliable meta-analysis. Therefore, we present the data from these papers using only descriptive statistics in Tables 5 and 6.

Comparison with $^{111}$In-octreotide (Octreoscan) (Summary Statistics)

There were 2 eligible papers (Table 5) that reported comparison of $^{68}$Ga-DOTATOC PET/CT with $^{111}$In-octreotide Single Photon Emission Computed Tomography (SPECT) imaging (3,24). All of the patients had known NET. Analysis in both papers was performed on a lesion by lesion basis. Sensitivity of $^{68}$Ga-DOTATOC on a per lesion basis was 100% and for $^{111}$In-octreotide was 78%.
Typical and Atypical Carcinoids (Summary Statistics)

There were 2 eligible papers (Table 6) that reported the performance of $^{68}$Ga-DOTATOC PET/CT in detecting pulmonary carcinoid tumors in 46 patients ($^{14,16}$). This tumor is addressed separately because of the generally lower somatostatin receptor density on typical (well-differentiated) and atypical (poorly differentiated) carcinoids. Grouped sensitivity was 100% for typical carcinoids and 83% for atypical.

Brief summaries of all the references are provided in Appendix 3.
DISCUSSION

There is a remarkable breadth in the medical literature addressing the efficacy of $^{68}$Ga-
DOTATOC PET in the evaluation of neuroendocrine tumors (NETs). All of the papers are from
outside the United States, since regulatory limitations are less restrictive elsewhere. Many of the
studies are done retrospectively and most of the papers have selection bias, often only imaging
patients who have biopsy-proven NET. This bias is largely inconsequential as the population
studied is representative of the population that will typically be clinically imaged. The reference
standard across papers is variable and it unfortunately often includes the results from the $^{68}$Ga-
DOTATOC PET imaging. This is an inherent problem in the setting when the new agent is far
better than any existing non-invasive test. The only reliable, objective reference standard is
histopathology after biopsy. Several papers use limited biopsy information, but it is ethically and
practically impossible to biopsy all the lesions that are seen.

Trial design in these papers is also widely varied. Some address the accuracy of the
methodology, but most address other aspects, including effect on subsequent management, how
the information can be combined with other imaging modalities, i.e. CT and Magnetic
Resonance Imaging (MRI), and the utility of $^{68}$Ga-DOTATOC PET for diagnosing disease in
patients with typical symptoms and biomarker findings. Many papers have multiple groups of
patients with different indications.

In spite of the broad variety, the results of the meta-analysis are generally consistent,
showing excellent sensitivity and specificity, frequent change of management after the scan, and
a high success rate in finding unknown primaries in patients with metastatic disease.

The results of this meta-analysis show a pooled sensitivity for detection of NETS with
$^{68}$Ga-DOTATOC of 92% and specificity of 82%. This is very similar to the results of an earlier,
smaller meta-analysis (25), where they found a pooled sensitivity of 93% and specificity of 85%. In addition, the sensitivity in this meta-analysis is identical to the value found in two meta-analyses of ⁶⁸Ga somatostatin receptor ligands (DOTATOC, DOTATATE, and DOTANOC combined) (26, 27). The specificity in the combined meta-analyses is somewhat higher, 96% in one and 93% in the other.

The sensitivity of ⁶⁸Ga-DOTATOC PET is definitely better than ¹¹¹In-octreotide SPECT imaging. In the 2 papers that directly compared the two approaches, the sensitivity for ⁶⁸Ga-DOTATOC on a per lesion basis was 100% and for ¹¹¹In-octreotide was 78%. In the package insert for ¹¹¹In-pentetreotide the reported sensitivity is 85.7% and specificity is 50% (28).

Because determination of sensitivity and specificity is very dependent on patient selection and the reference standard, it may be more appropriate to look at change in patient management as a more practical measure of efficacy than sensitivity and specificity. In this review 3 papers were found that reported change in management after ⁶⁸Ga-DOTATOC PET imaging. The pooled result was reported change of management in 95/188 (51%), which clearly illustrates the clinical significance of ⁶⁸Ga-DOTATOC imaging. A recent meta-analysis of the three common ⁶⁸Ga somatostatin receptor ligands combined, found an average of 44% change of management after imaging (29). This is somewhat higher than the results from the National Oncologic PET Registry study, which found that, following ¹⁸F-FDG imaging there was a change in management an average of 36.5% (30).

A unique indication for ⁶⁸Ga-DOTATOC PET imaging of NETs is in the setting when a patient presents with multiple sites of metastatic NET, typically in the liver and the site of the primary tumor is unknown. The issue of the need to resect the primary is controversial, but a systematic review of this issue found that 5-year survival was 72% for resected patients vs. 35%
for unresected (31). The 6 reviewed papers almost certainly suffered from patient selection bias, but the difference is so large that many surgeons feel that it is very appropriate to resect the primary, if it can be found. In this review there were four papers that reported on the success rate in finding unknown primaries with $^{68}$Ga-DOTATOC PET imaging, typically when other imaging approaches have failed. The overall success rate was 40 of 91 or 43.9%.

There are two settings where $^{68}$Ga-DOTATOC PET imaging of NETs is less successful, e.g. in atypical carcinoid and in patients who present with carcinoid syndrome symptoms (flushing and diarrhea) and elevated biomarkers. Atypical carcinoid tumors are more poorly differentiated than typical carcinoids and have significantly fewer somatostatin receptors. This is a well-known problem and it is recognized that $^{18}$F-FDG imaging is more effective in this setting. Apparently, although many patients with NETs have typical carcinoid syndrome symptoms, the converse is not true. There are many other etiologies of such symptoms. In 3 papers with 53 patients the overall yield was 7 true positives (13%) and one false positive.
CONCLUSION

$^{68}$Ga-DOTATOC is useful for evaluating the presence and extent in disease for staging, restaging, and to assist in treatment decision making for patients with NET. It is also effective in locating the site of an unknown primary in NET patients that present with metastatic NET, but no known primary tumor. It also appears to be more accurate than $^{111}$In-octreotide. Although $^{68}$Ga-DOTATOC would seem to be useful in evaluating patients with suggestive symptoms and biomarker findings, it does not perform well in this setting and has low yield. Overall, it appears to be an excellent imaging agent to assess patients with known NET and frequently leads to a change in management.

DISCLOSURE

We thank the Petersen Foundation for financial support. The authors have no other relevant conflicts of interest to report.
REFERENCES


FIGURES

Databases searched: MEDLINE/PubMed, Embase.com, Cochrane Register of Diagnostic Test Accuracy Studies, Cochrane Central Register of Controlled Trials (CENTRAL)

Search terms: (68Ga OR Ga-68 OR Ga-68 OR Ga OR gallium) AND DOTATOC

468 records located

Articles categorized by topic:
1. Chemistry
2. Clinical trial
3. Review
4. Animal study
5. Dosimetry
6. Cost effectiveness
7. PRRT
8. Case report
9. Not NET tumor
10. Technical detail
11. Clinical management
12. Other
13. RT planning

Discarded all except those categorized as
2. Clinical trials
6. Cost-effectiveness
10. Technical detail
4. Clinical management

382 records discarded

86 records

Abstracts read to determine relevance of article to:
1) Sensitivity/Specificity
2) Change in management
3) Unknown primary
4) 111In pentetreotide comparison
5) Diagnosis of NET

46 records discarded

40 records

Articles read in full. Rejected for:
1) Per lesion analysis only (9)
2) DOTATOC only reference standard (1)
3) Anomalous tumor type (1)
4) Non-standard imaging methodology (1)
5) Poor quality data (1)
6) Duplicates & abstracts (10)

23 records discarded

17 records

Articles included in meta-analysis, categorized as:
1) Sensitivity/Specificity (12)
2) Change in management (4)
3) Unknown primary (4)
4) 111In pentetreotide comparison (2)
5) Diagnosis of NET (3)
(Some articles had data for more than one category)

QUADAS rating used to help guide selection

Figure 1. Study Flow Diagram
### Figure 2. Sensitivity and Specificity forest plot.

<table>
<thead>
<tr>
<th>Individual papers</th>
<th>Counts</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>TP</td>
<td>FN</td>
<td>TN</td>
</tr>
<tr>
<td>Gabriel, 2007</td>
<td>84</td>
<td>69</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Verisf, 2010</td>
<td>19</td>
<td>12</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Ruf, 2011</td>
<td>51</td>
<td>32</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Mayerhofer, 2012</td>
<td>55</td>
<td>32</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Beidenwellen, 2013</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Schraml, 2013</td>
<td>51</td>
<td>40</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Venkitaraman, 2014</td>
<td>32</td>
<td>25</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td><strong>300</strong></td>
<td><strong>214</strong></td>
<td><strong>14</strong></td>
<td><strong>62</strong></td>
</tr>
</tbody>
</table>

- TP: True Positive
- FN: False Negative
- TN: True Negative
- FP: False Positive
Figure 3. Diagnostic odds ratio forest plot.

The total diagnostic odds ratio for these papers is 60.80 (17.07, 216.60).

The table lists log (base e) ratios.
**Figure 4.** Change of management forest plot.

<table>
<thead>
<tr>
<th>Individual papers</th>
<th>Counts</th>
<th>Change of management</th>
<th>Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>COM</td>
<td>No COM</td>
</tr>
<tr>
<td>Ruf, 2010</td>
<td>64</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Filling, 2010</td>
<td>52</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Froeling, 2012</td>
<td>21</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Schram, 2013</td>
<td>51</td>
<td>30</td>
<td>21</td>
</tr>
</tbody>
</table>

**Summary**

| Total             | 188    | 95       | 93        | 0.51 (0.39, 0.62) |
## TABLES

<table>
<thead>
<tr>
<th>Paper</th>
<th>Diagnosis</th>
<th>Sensitivity &amp; Specificity</th>
<th>Unknown Primary</th>
<th>Change in Management</th>
<th>Comp. with Octreoscan</th>
<th>Carcinoid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofmann 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Buchman 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Gabriel 2007</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frilling 2010</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruf 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Versari 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jindal 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Kumar 2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poeppel 2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruf 2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Froeling 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Mayerhoefer 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beiderwellen 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schraml 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Schreiter 2014</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Venkitaraman 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Nakamoto 2015</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menda 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Table 1.** Qualified literature data available and used for sub-analysis of each of the six identified indications or clinical settings.
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>TP</th>
<th>FN</th>
<th>TN</th>
<th>FP</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabriel 2007</td>
<td>84</td>
<td>69</td>
<td>2</td>
<td>12</td>
<td>1</td>
<td>97.2%</td>
<td>92.3%</td>
</tr>
<tr>
<td>Versari 2010</td>
<td>19</td>
<td>12</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>92.3%</td>
<td>83.3%</td>
</tr>
<tr>
<td>Ruf 2011</td>
<td>51</td>
<td>32</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>82.1%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Mayerhoefer 2012</td>
<td>55</td>
<td>32</td>
<td>1</td>
<td>18</td>
<td>4</td>
<td>97.0%</td>
<td>81.8%</td>
</tr>
<tr>
<td>Beiderwollen 2013</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>80.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Schraml 2013</td>
<td>51</td>
<td>40</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>97.6%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Venkitaraman 2014</td>
<td>32</td>
<td>25</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>96.2%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Frilling 2010</td>
<td>52</td>
<td>52</td>
<td>0</td>
<td></td>
<td></td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Poeppel 2011</td>
<td>40</td>
<td>40</td>
<td>0</td>
<td></td>
<td></td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Jindal 2011</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td></td>
<td></td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Kumar 2011</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Nakamoto 2015</td>
<td>46</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
<td>85.7%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Sensitivity and Specificity**
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>TP Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frilling 2010</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Schreiter 2014</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Nakamoto 2015</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Menda 2017</td>
<td>40</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 3.** Identification of Unknown Primary
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>TP</th>
<th>FN</th>
<th>TN</th>
<th>FP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabriel 2007</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Schreiter 2014</td>
<td>19</td>
<td>2</td>
<td>0</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Nakamoto 2015</td>
<td>25</td>
<td>1</td>
<td>0</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4.** Diagnosis in patients suspected to have NET
<table>
<thead>
<tr>
<th>Authors</th>
<th>DOTATOC</th>
<th>Octreotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>TP</td>
<td>FN</td>
</tr>
<tr>
<td>Hofmann 2001</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Buchman 2007</td>
<td>27</td>
<td>70</td>
</tr>
</tbody>
</table>

**Table 5.** $^{68}$Ga-DOTATOC vs. $^{111}$In-Octreotide
(In both studies the reported evaluation is lesion-by-lesion)
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>TP</th>
<th>FN</th>
<th>TP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jindal 2010</td>
<td>20</td>
<td>13</td>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Venkitaraman 2014</td>
<td>26</td>
<td>21</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 6.** Typical vs Atypical Carcinoid Tumors
Appendix 1

Ga-68 Article Abstraction Form

Article ID: ________________________________

N: __________ Country: _____________ Age Range: _____________
or Ave Age: __________

Tumor type (s)
☐ Gastroenteropancreatic NET  ☐ Paraganglioma
☐ Carcinoid  ☐ Liver metastases / unknown primary
☐ NET not otherwise defined

Reference Standard
☐ Histology  ☐ Other Imaging (CT, MRI)  ☐ Not well defined
☐ Consensus (biased, i.e. includes DOTATOC)  ☐ Consensus (unbiased)

Interpretation Criteria
☐ Blinded (No information)  ☐ Blinded (Clinical info only)
☐ Unblinded (Aware of clinical and Imaging info)

Type of Article
☐ Sensitivity, Specificity, etc
☐ Comparison with In-111 Octreoscan
☐ Change of Management
☐ Unknown primary
☐ Diagnostic test (biochemical and/or clinical indication, but no known tumor)
☐ Peptide Radionuclide RadioTherapy (PRRT)

Sensitivity, Specificity, etc. & Comparison with In-111 Octreoscan

Change of Management
Overall % Change of management: ___ % major change: ___ % minor change: ___ ☐ Not stated

Unknown primary (UP)
Definition of UP: ____________________________________________ or ☐ Not defined
% Yield in finding UP: ________ or ☐ Not analyzed separately

Diagnostic test (biochemical and/or clinical indication, but no known tumor)

Appendix 2

DOTATOC Meta-analysis supplement
# QUADAS Article Abstraction Form

<table>
<thead>
<tr>
<th>Article:</th>
<th>Reviewer:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blinded Read</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not clearly described</td>
<td>Unblinded</td>
</tr>
</tbody>
</table>

| 2: Reference Standard | |
| Not clearly described | Biased consensus (uses DOTATOC information) | Other Imaging (i.e., CT and/or MRI) | Unbiased consensus (no DOTATOC information used) | Histology |

| 3: Reference Standard (Comparison only) | |
| No reference standard | Imaging-based Bias with DOTATOC | Imaging-based unbiased – no DOTATOC | Histology |

| 4. Patient Selection/Inclusion Criteria (Sensitivity/Specificity) | |
| Not clearly described | Patients selected by somatostatin receptor imaging | Biased: Patients with only histologically proven NET disease | Consecutive patients referred for DOTATOC – particular NET disease | Consecutive patients referred for DOTATOC – all reasons or other unbiased methods |

| 4. Patient Selection/Inclusion Criteria (Comparison with other radiotracers) | |
| Not clearly described | Biased by lesion size, previous study with other radiotracer, or other imaging bias | Biased by disease type or other limiting characteristic | Consecutive patients referred for DOTATOC or Octreoscan or other unbiased method |

| 5. Patient Selection/Inclusion Criteria (Change in Management) | |
| Not clearly described | Patients with only histologically proven NET | Consecutive patients referred for DOTATOC – particular NET disease | Consecutive patients referred for DOTATOC – all reasons or other unbiased methods |

| 6. General Study Design | |
| Not clearly described | Retrospective | Prospective/Retrospective mixed | Prospective |

| 7. Image Interpretation Criteria | |
| Not clearly described | Methodologies for interpreting only ancillary imaging (CT, MRI) well described | Methodologies for interpreting only DOTATOC well described | Methodologies for interpreting all imaging |

General Comments:
Appendix 3

Brief summaries of the references

• Hofmann et al, 2001 (3). Title: “Biokinetics and imaging with the somatostatin receptor PET radioligand $^{68}$Ga-DOTATOC: preliminary data”. Prospective. This was the first published paper on $^{68}$Ga-DOTATOC imaging in patients. N = 8 patients with known metastatic carcinoid tumors. All patients had positive $^{111}$In-octreotide scans prior to PET imaging. $^{68}$Ga-DOTATOC PET imaging identified NET lesions in all patients. In every patient $^{68}$Ga-DOTATOC showed more lesions than $^{111}$In-octreotide.

• Gabriel et al. 2007 (8). Title: “$^{68}$Ga-DOTA-Tyr$^3$-Octreotide PET in Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and CT”. Prospective. N = 84. Patients with known or suspected NET. The reference standard was based on all available histologic, imaging, and follow-up findings. Group 1. Suspected NET with symptoms and elevated biomarkers, but no evidence of disease by conventional imaging (N = 13); Group 2. Initial tumor staging (N = 36); Group 3. Follow-up after therapy (N = 35). Each patient was also imaged with $^{99m}$Tc-HYNIC-TOC and $^{111}$In-DOTATOC. Neither of these agents is widely used, and this comparison was not useful for the present analysis. In Group 1, there were 5 positives, including one false positive. In Group 2 sensitivity was 97% and specificity was 100%. In Group 3 sensitivity was also 97% and specificity was 100%.

• Versari et al, 2010 (9). Title: “Ga-68 DOTATOC PET, Endoscopic Ultrasonography, and Multi-detector CT in the diagnosis of duodenopancreatic neuroendocrine tumors”. Retrospective. N = 19 patients suspected to have duodenopancreatic primitive NET. The reference standard was fine needle biopsy and/or surgery. On a per-patient basis, sensitivity for Ga-68 DOTATOC was 12/13 (92%) and specificity was 5/6 (83%).
• Ruf et al, 2011 (10). Title: "$^{68}$Ga-DOTATOC PET/CT of Neuroendocrine Tumors: Spotlight on the CT Phases of a Triple-Phase Protocol". Retrospective. N = 51 patients with known or suspected NET. The reference standard was clinical and imaging follow-up, histopathology (if available), and the decision of an interdisciplinary truth-panel. On a per-patient basis, sensitivity for Ga-68 DOTATOC was 32/39 (82%) and specificity was 8/12 (67%).

• Mayerhofer et al, 2012 (11). Title: “Are contrast media required for (68)Ga-DOTATOC PET/CT in patients with neuroendocrine tumours of the abdomen?”. Retrospective. N = 55. Patients with known or suspected NETs of the abdomen. The reference standard was a combination of histology reports, reports of other imaging examinations (MRI, ultrasound), or reports of follow-up PET/CT or CT performed 3–6 months after the original PET/CT. There were two 2-man teams of interpreters, junior and senior teams. Studies were done both with and without CT contrast. Image evaluation was completely blinded and was reported on a “per-region” basis. For un-enhanced PET/CT imaging sensitivity was 89.3% for the junior team and 92.0% for the senior team. Specificity was 99.1% for the junior team and 99.2% for the senior team. Performance improved slightly with contrast enhanced images. Results were also reported on a “per-patient” basis, and the results from the senior team were used in the combined summary in this paper.

• Beiderwellen et al, 2013 (12). Title: “Simultaneous $^{68}$Ga-DOTATOC PET/MRI in Patients With Gastroenteropancreatic Neuroendocrine Tumors Initial Results”. Prospective. N = 8. Patients all had histopathologically confirmed NET. The reference standard was clinical imaging, existing prior examinations, and histopathology (if available). Five of the eight patients had malignant NET lesions at the time of the examination. $^{68}$Ga-DOTATOC PET alone identified 4 of the 5 patients as positive. $^{68}$Ga-DOTATOC PET/MRI identified all 5.
- Schraml et al, 2013 (13). Title: “Staging of neuroendocrine tumours: comparison of [68Ga]DOTATOC multiphase PET/CT and whole-body MRI”. Prospective. N = 51. Patients had histologically proven NET and suspicion of metastases. All patients were imaged with [68Ga]DOTATOC-PET/CT and separately with whole-body MRI. Reference standard was based on correlation of all imaging data, histologic and surgical findings, and clinical follow-up. The sensitivity for [68Ga]DOTATOC-PET/CT was 98% (40/41) and the specificity was 100% (10/10).

- Venkitaraman et al, 2014 (14). Title: “Role of 68Ga-DOTATOC PET/CT in initial evaluation of patients with suspected bronchopulmonary carcinoid”. Prospective. N = 32. Patients had clinical suspicion of bronchopulmonary carcinoid studied using 68Ga-DOTATOC and 18F-FDG. The combined results from the two types of study were used as the reference standard. Based on the reference standard, 26 cases of carcinoid were found (21 typical and 5 atypical). The sensitivity of 68Ga-DOTATOC was 100% for typical and 80% for atypical carcinoid.

- Frilling et al, 2010 (15). Title: “The Impact of 68Ga-DOTATOC Positron Emission Tomography/Computed Tomography on the Multimodal Management of Patients With Neuroendocrine Tumors”. Retrospective. N = 52. All patients had histologically proven NET. The reference standard was based on intraoperative findings, histopathologic reports, and follow-up data of at least 6 months. Sensitivity on a per-patient basis was 100%. They eliminated 7 of 15 patients being evaluated for liver transplantation, because of evidence of metastatic deposits not seen by conventional imaging. Overall, 68Ga-DOTATOC PET/CT altered treatment management decisions, previously based on CT and/or MRI alone, in 31 (60%) of the 52 patients.

- Jindal et al, 2010 (16). Title: “Role of 68Ga-DOTATOC PET/CT in the Evaluation of Primary Pulmonary Carcinoids”. Retrospective. N = 20. Patients had typical (13) and atypical (7) carcinoids. DOTATOC PET/CT detected all the typical carcinoids and 6/7 of the atypical. Typical carcinoids showed significantly higher levels of DOTATOC uptake than atypical carcinoids.
• Kumar et al, 2011 (17). Title: “Role of $^{68}$Ga-DOTATOC PET-CT in the diagnosis and staging of pancreatic neuroendocrine tumours”. Prospective. N = 20. Patients had clinically suspected and/or histopathologically proven pancreatic NET. The reference standard was histopathology for primary tumor and clinical follow up with MRI and/or biopsy. Sensitivity on a per-patient basis was 100%.

• Nakamoto et al, 2015 (18). Title: “Additional information gained by positron emission tomography with $^{68}$Ga-DOTATOC for suspected unknown primary or recurrent neuroendocrine tumors”. Retrospective. N = 46: Group 1: Known NET metastatic disease with unknown primary (N = 14); Group 2: Looking for recurrent NET after curative treatment, with negative imaging, but with high biomarker levels (N = 7); Group 3: Suspected NET because of high biomarker levels (N = 25). The reference standard was histopathological confirmation or clinical follow-up for at least 6 months. In Group 1 they found 7 unknown primaries with one false positive. In Group 2 they found disease in 6. In Group 3 they found one site of disease.

• Poeppel et al, 2011 (19). Title: “$^{68}$Ga-DOTATOC Versus $^{68}$Ga-DOTATATE PET/CT in Functional Imaging of Neuroendocrine Tumors”. Prospective. N = 40. All patients had documented NETs as part of workup for possible peptide receptor radionuclide therapy. Reference standard was histology. Sensitivity on a per-patient basis was 100%. $^{68}$Ga-DOTATOC found slightly more lesions than $^{68}$Ga-DOTATATE (262 vs. 254). The average primary tumor standardized uptake Value (SUV) was somewhat higher with $^{68}$Ga-DOTATOC than with $^{68}$Ga-DOTATATE (33 ± 22 vs. 18 ± 12). The conclusion was “$^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE possess a comparable diagnostic value in the detection of lesions of NETs, with a potential advantage for $^{68}$Ga-DOTATOC”.

DOTATOC Meta-analysis supplement
• Froeling et al, 2012 (20). Title: “Impact of Ga-68 DOTATOC PET/CT on the diagnosis and treatment of patients with multiple endocrine neoplasia (MEN)”. Retrospective. N = 21. All patients had MEN. The reference standard was histopathologic proof or by clinical and radiologic follow-up. Ga-68 DOTATOC PET/CT findings led to a change in treatment in 10 of 21 (48%) patients. NET lesions were detected in all patients. On a lesion-by-lesion basis Ga-68 DOTATOC had a sensitivity of 92 % and specificity of 94 %.

• Ruf et al, 2010 (21). Title: “Impact of Multiphase 68Ga-DOTATOC-PET/CT on Therapy Management in Patients with Neuroendocrine Tumors”. Retrospective. N = 64. Patients had known or suspected NET. The reference standard was based on the results of combined PET and CT imaging, follow-up documentation by the department of gastroenterology, and the decision of the interdisciplinary tumor board. There were 50 true positives and 14 true negatives by 68Ga-DOTATOC imaging. The major goal of the study was to determine the impact of 68Ga-DOTATOC on patient management. 68Ga-DOTATOC-PET/CT had a significant impact on therapeutic management in 24/64 (38%) of all NET patients.

• Schreiter et al, 2014 (22). Title: “Searching for primaries in patients with neuroendocrine tumors (NET) of unknown primary and clinically suspected NET: Evaluation of Ga-68 DOTATOC PET/CT and In-111 DTPA Octreotide SPECT/CT”. Retrospective. N = 123: Group 1: metastatic NET with unknown primary (N = 83) Group 2: clinically suspected NET (N = 40). The reference standard was histopathology or clinical verification based on follow-up. Most patients only had Ga-68 DOTATOC or In-111 Octreotide scans but not both. 20 patients had both but were not analyzed separately. In Group 1 Ga-68 DOTATOC detected primaries in 15 patients (46%) and In-111 Octreotide in 4 patients (8%). In Group 2 only two primaries were detected, both with Ga-68 DOTATOC.
• Menda et al. 2017 (23). Title: “Localization of Unknown Primary Site with $^{68}$Ga-DOTATOC PET/CT in Patients with Metastatic Neuroendocrine Tumor”. Prospective. N=40. Patients with proven metastatic NET and unknown primary. Image evaluation: True positive (TP) was confirmation by biopsy or follow-up imaging. False positive (FP) if no primary lesion was found at site of uptake. Negative scans were classified as false negative (FN). Unconfirmed (UC) was a positive scan but no histology or follow-up imaging. Results: The TP, FP, FN and UC rates for unknown primary tumor were 38%, 7%, 50% and 5% respectively. Conclusion: $^{68}$Ga-DOTATOC PET/CT is an effective modality in localization of unknown primary in patients with metastatic NET.

• Buchman et al, 2007(24). Title: “Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours”. Prospective. N = 27. All patients had histologically proven NETs. Results were compared with $^{111}$In-octreotide. The reference standard was based on histopathology, MRI, or CT. Lesions were seen in all patients with both modalities. On a regional basis 52 regions were verified positive by $^{68}$Ga-DOTATOC PET. 18 of these regions were missed by $^{111}$In-octreotide. There were no regions identified by $^{111}$In-octreotide that were missed with $^{68}$Ga-DOTATOC PET.
68Ga-DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Meta-Analysis

Michael M. Graham, Xiaomei Gu, Timothy Ginader, Patrick Breheny and John Sunderland

J Nucl Med.
Published online: March 9, 2017.
Doi: 10.2967/jnumed.117.191197

This article and updated information are available at: http://jnm.snmjournals.org/content/early/2017/03/08/jnumed.117.191197

Information about reproducing figures, tables, or other portions of this article can be found online at: http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at: http://jnm.snmjournals.org/site/subscriptions/online.xhtml

JNM ahead of print articles have been peer reviewed and accepted for publication in JNM. They have not been copyedited, nor have they appeared in a print or online issue of the journal. Once the accepted manuscripts appear in the JNM ahead of print area, they will be prepared for print and online publication, which includes copyediting, typesetting, proofreading, and author review. This process may lead to differences between the accepted version of the manuscript and the final, published version.