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Evidence-Based Series 12-13

Radionuclide Therapy for Neuroendocrine Malignancies

K.Y. Gulenchyn, X. Yao, S.L. Asa, S. Singh, C. Law,
and members of the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel

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

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https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1356

Section 1: Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-Based Series 12-13: Section 1

Radionuclide Therapy for Neuroendocrine Malignancies: Guideline Recommendations

K.Y. Gulenchyn, X. Yao, S.L. Asa, S. Singh, C. Law,
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QUESTIONS

1. What are the effects of the eight commonly used and studied therapeutic radiopharmaceuticals described in Table 1 below in patients with different types of neuroendocrine malignancies?
2. Which one of the eight therapeutic radiopharmaceuticals is most effective in improving clinical outcomes (i.e., tumour response, duration of tumour response, overall survival [OS] time/rate, progression-free survival [PFS] time/rate, biochemical response, and quality of life [QOL]) in the above patients?
3. What are the toxicities for each therapeutic radiopharmaceutical?

Table 1. Radiopharmaceuticals considered by this practice guideline.

Name	Alternate name
^{111}In-DTPAOC	[^{111}In-DTPA^{0}]octreotide, ^{111}In-DTPA-D-Phe-octreotide, ^{111}In-pentetreotide
^{111}In-DOTATATE	^{111}In -DOTA-TYR^{3}-octreotate, ^{111}In-octreotate
^{90}Y-DOTATOC	^{90}Y-DOTA-TYR^{3}-octreotide, ^{90}Y-SMT487, ^{90}Y-edotreotide
^{90}Y-DOTALAN	^{90}Y-DOTA-lanreotide
^{90}Y-DOTATATE	^{90}Y-DOTA-TYR^{3}-octreotate, ^{90}Y-octreotate
^{177}Lu-DOTATOC	^{177}Lu-DOTA-TYR^{3}-octreotide, ^{177}Lu-octreotide
^{177}Lu-DOTATATE	^{177}Lu-DOTA-TYR^{3}-octreotate, ^{177}Lu-octreotate
^{131}I-MIBG	^{131}I-metaiodobenzylguanidine, ^{131}I-iobenguane

TARGET POPULATION

These recommendations apply to neuroendocrine cancer patients who are inoperable, or have residual disease following surgery or other ablative therapy, or have metastases.

INTENDED USERS

This guideline is intended for nuclear medicine physicians, medical oncologists, surgeons, and pathologists who are involved in the treatment of the above-targeted patients.

INTRODUCTION

Neuroendocrine tumours (NETs) constitute a heterogeneous group of neoplasms: they include epithelial neuroendocrine carcinomas originating in multiple sites throughout the body as well as tumours of modified neurons arising in sympathetic or parasympathetic ganglia and the adrenal medulla (1,2). The latter express tyrosine hydroxylase to synthesize dopamine and, therefore, readily take up ^{131}I- and ^{123}I-MIBG; however, the former express somatostatin receptors as a distinguishing feature and are amenable to ablation with radiolabeled somatostatin analogues (1,2). Although therapy with both MIBG and radiolabeled somatostatin analogues has been provided in Ontario, it has not been made broadly available: barriers to access have resulted in out-of-country requests. A systematic review was conducted to inform the recommendations for the selection of agents for therapy and to inform the development of criteria for access to radionuclide therapies for NET patients in Ontario. The details of the method and results of this systematic review are shown in Section 2. There are no randomized controlled trials (RCTs) examining the effectiveness of any of the peptide receptor radionuclide therapy (PRRT) agents or ^{131}I-MIBG in the treatment of neuroendocrine cancer patients. Trials have not been conducted to compare either PRRT or ^{131}I-MIBG with placebo, systemic therapy, tumour debulking treatment, or long-acting somatostatin analogues. Furthermore, no trials have been conducted to make direct comparisons between or among the eight agents reviewed.

RECOMMENDATIONS AND KEY EVIDENCE

The Expert Panel and the Working Group offer the following recommendations based on the evidence reviewed:

- PRRT appears to be an acceptable option in adult patients with neuroendocrine cancer who are inoperable, have residual disease following surgery or other ablative therapy, or have metastases. PRRT is relatively safe and well tolerated with renal protection using lysine and arginine amino acid solution, especially for ^{90}Y-DOTALAN and ^{177}Lu-DOTATATE. However, renal function must be monitored.
- Treatment with PRRT in Ontario should be conducted as part of one or more RCTs, or in large comparative clinical trials if an RCT is not feasible, under the authority of a Clinical Trials Agreement, to clarify the further effects of PRRT (for example, comparing ^{177}Lu-DOTATATE with sunitinib in an RCT).
- ^{131}I-MIBG may be effective for malignant neuroblastoma, paraganglioma, or pheochromocytoma, but there is insufficient evidence to suggest its efficacy for adult neuroendocrine carcinoma patients. However, the hematologic toxicity, severe infections, and secondary malignancies possible afterwards should be considered.

Qualifying Statements

- There is limited evidence, based on a historical comparison of studies from a single centre (see Key Evidence below), that ^{177}Lu-DOTATATE may be associated with greater OS, PFS, and overall response rate (defined as the sum of complete response, partial response, and minor response rates) compared with ^{90}Y-DOTATOC or ^{111}In-DTPAOC. Therefore, ^{177}Lu-DOTATATE would be an appropriate agent to include in the future clinical trials described above.

- Prior to the administration of therapy, the tumours from NET patients who are to receive PRRT or ^{131}I-MIBG should demonstrate a positive uptake of the related diagnostic agent.
- A recommendation cannot be made for or against the use of PRRT in early-stage NET patients, as there is no relevant evidence.

Key Evidence

Peptide Receptor Radionuclide Therapy

- Fifteen prospective single-arm articles (3-17) and one prospective comparative study (18) met the study selection criteria; of the nine published after 2005, all investigated the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, or ^{177}Lu-DOTATATE (9-17). The total sample size was 1179. All the patient tumours showed a higher or the same uptake on octreoscan than on liver uptake before PRRT. All but one study (12) reported the overall response rate as determined by three different imaging criteria in a variety of stage III-IV NET subgroups. Across all agents, overall response rates ranged from 5% to 75% in various tumour subgroups, with wide 95% confidence intervals (CI) (See Figure 2 in Section 2).
- Three studies were conducted in the same clinical centre to investigate the effects of ^{111}In-DTPAOC, ^{90}Y-DOTATOC, and ^{177}Lu-DOTATATE at different time periods (5,10,13). The median OS and PFS time was 37 and 14 months, respectively, for ^{90}Y-DOTATOC at five-year follow-up (10), and 46 and 33 months, respectively, for ^{177}Lu-DOTATATE at four years (14). The overall response rate was 18% (CI, 6% to 30%) for patients with progressive stage III-IV NET treated with ^{111}In-DTPAOC, 21% (CI, 11% to 31%) for patients with stage III-IV neuroendocrine gastroenteropancreatic tumours (GEP-NET) treated with ^{90}Y-DOTATOC, and 46% (CI, 40% to 52%) for patients with stage IV GEP-NET disease treated with ^{177}Lu-DOTATATE.
- Eight of the 16 articles reported survival outcomes, with six reporting median OS times ranging from 15 to 46 months for various stage III-IV NET subgroups (10,11,13,15-17). There was no significant difference in OS time between the intervention (14 patients treated with ^{111}In-DTPAOC and five patients treated with ^{131}I-MIBG) and control arm in the unique comparative trial (18).
- Of the fifteen articles that reported on toxicity, 11 specified one of two criteria used for grading toxicity. Nausea and vomiting were common during therapy. The severe toxicities included the following: for ^{111}In-DTPAOC, 8% of patients developed myelodysplastic syndrome (MDS) and/or leukemia in one study (5); for ^{90}Y-DOTATOC, 0.9% to 3.4% of patients developed grade 4 renal toxicity in three studies (9-11), with 2% of patients developing MDS in one study (10); for ^{90}Y-DOTALAN, no severe toxicity was found in one study (6); for ^{90}Y-DOTATATE, 30% of patients developed grade 2 renal toxicity at two years in one study (16); and for ^{177}Lu-DOTATATE, 0.6% of patients developed hepatic insufficiency, 0.8% developed MDS, and 0.4% developed renal insufficiency in one study (13). For studies investigating the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, and ^{177}Lu-DOTATATE, lysine and arginine amino acid solution was infused to protect kidney function.

^{131}I-MIBG Therapy

- Six prospective single-arm, one retrospective comparative, and one retrospective single-arm study examining the effectiveness of ^{131}I-MIBG were eligible; the total sample size was 612. All the patients showed at least one lesion as positive on the ^{123}I-MIBG or ^{131}I-MIBG scintigraphy. The overall tumour response rate on imaging by various imaging criteria ranged from 32% to 75% for stage III-IV pediatric neuroblastoma patients with a median age of 2.0 to 6.6 years old (19-23) and was 26% for adult and stage III-IV NET patients (24) (including 22 neuroblastomas, 10 pheochromocytomas, three paragangliomas, six medullary thyroid carcinomas, and four carcinoids) and 27% for

patients with stage IV paraganglioma or pheochromocytoma (25) (See Figure 3 in Section 2).

- The Sywak et al study was the unique comparative study for comparing standard therapies alone with standard therapies plus ^{131}I-MIBG in stage IV patients with midgut carcinoid (26). The OS rate was 63% (CI, 47% to 75%) in the intervention group and 47% (CI, 34% to 59%) in the control group at five years, without statistical significance (p=0.10).
- Of seven studies reporting on toxicity, three used different criteria, and four studies did not specify the criteria for toxicity grading. Hematologic toxicities were the main severe side effects. Forty-three percent of patients had bone marrow replacement (BMR), and one patient developed secondary leukemia in one study (19). Five percent of patients in one study (20) and 2% of patients in another study (22) developed leukemia or MDS. In a retrospective study, five (4%) three- to five-year-old neuroblastoma patients developed secondary malignancies after ^{131}I-MIBG therapy either as part of first-line therapy or as salvage therapy for resistant or recurrent disease: one acute nonlymphoblastic leukemia at one and a half years, one chronic myelomonocytic leukemia at four years, one malignant schwannoma at seven years, one rhabdomyosarcoma at 14 years, and one angiomatoid malignant fibrous histiocytoma at 10 years after ^{131}I-MIBG (21). In a fifth study, 39% of patients needed autologous BMR, and 9% of patients died (23) where ^{131}I-MIBG was utilized as the first-line treatment. Forty-one percent of patients had grade 2-3 hematologic toxicities in a sixth study (24). After an accumulative dose of at least 63.3 gigabecquerels (GBq) ^{131}I-MIBG therapy, 4% of patients who did not have prior radiation or chemotherapy developed MDS and acute myeloid leukemia at two and five years, respectively, in the seventh study (25). In addition, 4% of patients in that same study developed acute respiratory distress syndrome, 4% developed bronchiolitis obliterans organizing pneumonia, and 2% had a pulmonary embolism.

Treatment Alternatives

An RCT has shown somatostatin analogs to be more effective than placebo in the control of tumour growth in patients with metastatic midgut NETs (27).

Recently, investigators of two studies have reported positive results in the use of biologic agents for the treatment of malignant pancreatic NETs: one was the tyrosine kinase inhibitor sunitinib, and the other was the mTOR (mammalian target of rapamycin) inhibitor, everolimus (28,29). Both trials were phase III, multicentre, double-blind, randomized, placebo-controlled trials with sufficient numbers of patients to yield clear statistical results. Sunitinib, as compared with placebo, caused more than a doubling in PFS (11.4 versus [vs.] 5.5 months, respectively, $p<0.001$). Everolimus caused a 65% reduction in the estimated risk of progression (PFS of 11.0 months for everolimus vs. 4.6 months for placebo, $p<0.001$).

FUTURE RESEARCH

The recent publications that report positive results with the biological agents of sunitinib, everolimus, and octreotide long-active release (LAR), particularly with regard to PRRT, raise many important questions that could be the subject of further investigation. Should these drugs be used before, after, or in combination with PRRT? Can these drugs be used alone or in combination with PRRT as adjuvant or neoadjuvant therapy (with surgery)? For malignant NET patients with negative uptake on octreoscan or renal insufficiency and positive uptake on ^{123}I-MIBG scintigraphy, does ^{131}I-MIBG work well? Furthermore, the use of PRRT early in the treatment of NET patients (i.e., before maximal medical treatment) has not been explored and should be an option for further study in Ontario.

The development of a standardized program for the assessment, treatment, and follow-up of NET patients in Ontario is essential to ensure the existence of an appropriate infrastructure for the evaluation of promising new therapies that would provide patients suffering from NETs with high-quality, evidence-based care.

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Evidence-Based Series 12-13: Section 2

Radionuclide Therapy for Neuroendocrine Malignancies: Evidentiary Base

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^{90}Y-DOTALAN	^{90}Y-DOTA-lanreotide
^{90}Y-DOTATATE	^{90}Y-DOTA-TYR^{3}-octreotate, ^{90}Y-octreotate
^{177}Lu-DOTATOC	^{177}Lu-DOTA-TYR^{3}-octreotide, ^{177}Lu-octreotide
^{177}Lu-DOTATATE	^{177}Lu-DOTA-TYR^{3}-octreotate, ^{177}Lu-octreotate
^{131}I-MIBG	^{131}I-metaiodobenzylguanidine, ^{131}I-iobenguane

INTRODUCTION

Neuroendocrine tumours (NETs) constitute a heterogeneous group of neoplasms originating from endocrine cells that secrete biogenic amines and polypeptide hormones.

These tumours derive from endocrine glands and include neuroendocrine carcinomas that arise in the pituitary, parathyroids, endocrine islets within the pancreas, and dispersed endocrine cells in the thyroid, respiratory system and gastrointestinal tract, as well as neuroendocrine tumours arising in sympathetic or parasympathetic ganglia and the adrenal medulla (1). The clinical behaviour of NETs is enormously variable: they may be hormonally active or endocrinologically non-functioning, and may range from very slow-growing tumours (well-differentiated NETs) to highly aggressive and very malignant tumours (poorly differentiated NETs) (2). Recently, the incidence of NETs has gradually increased worldwide. In terms of the data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database and the Norwegian Registry of Cancer (NRC), the overall Caucasian NET incidence was 4.44 per 100,000 in the United States and 3.24 per 100,000 in Norway from 1993-2004 (3). SEER and NRC, however, found a marked increase of 37-40% and 72%, respectively, in the period 2000-2004 compared with 1993-1997 in the two countries. Data from the Ontario Cancer Registry show that the incidence of NETs gradually increased from 2.59 per 100,000 in 2002 to 4.33 per 100,000 in 2007 for people over 15 years old (4). No matter what the cause of increasing incidence (such as improving diagnostic techniques), more NET patients will ultimately require appropriate treatment.

Surgery is currently the only available curative treatment for NET patients, but for patients who are inoperable, or who have residual disease or metastases, few therapeutic options are available. The OS time following various combinations of chemotherapy can be 12-24 months, but such therapies can have significant side effects and a negative impact on the QOL (5). Biotherapy with somatostatin analogs or interferon can improve symptoms caused by an excess of bioactive substances but rarely significantly reduces overall tumour size (6). Recently, octreotide long-acting release (a somatostatin analog) proved to lengthen time to tumour progression in patients with metastatic midgut NETs in a randomized controlled trial (RCT) (7), and two RCTs showed that two novel biologic agents (sunitinib and everolimus) were useful in malignant pancreatic NET patients (8,9).

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs has been identified as a promising therapeutic option, and seven therapeutic radiopharmaceuticals (Table 1) have been used to treat patients with NETs in the past decade. A number of small studies and case series have showed that PRRT has few serious adverse effects and is associated with improving important clinical outcomes such as tumour response and PFS (10). However, this evidence has never been systematically reviewed.

Another available radionuclide agent that has also been used for treating NETs since the late 1970s is ^{131}I-MIBG. Similarly to PRRT, there have been a number of studies in which ^{131}I-MIBG has shown some value in the treatment of certain NETs (e.g., pheochromocytomas or paragangliomas) (11). As with PRRT, this evidence also has never been systematically reviewed.

In Ontario, patients at the London Health Sciences Centre (LHSC) receive ^{111}In-DTPAOC and ^{131}I-MIBG alone and in combination with chemotherapy. The LHSC work has been the subject of four published abstracts between 2001 and 2006 (12-15) and three more recent, unpublished presentations. The most recent data available indicate that between October 2000 and July 2005, 344 therapy doses of ^{111}In-DTPAOC consisting of 3.7 gigabecquerel (GBq) at six-week intervals for up to nine doses have been administered, both with and without chemosensitization consisting of 5-fluorouracil, carboplatin, and epirubicin. However, these data have not been fully published, and toxicities were not reported. No information regarding the use of other therapeutic radiopharmaceuticals in Ontario is available.

To ensure that the most appropriate radiopharmaceuticals are safely used on the most appropriate patients and to ensure that NET patients across Ontario who are eligible for radionuclide therapy have equitable access to in-province treatment, Cancer Care Ontario

(CCO) and the Ministry of Health have requested a clinical practice guideline and systematic review based on the above research questions to guide clinicians on how best to implement and manage radionuclide therapy in malignant NET patients in Ontario. This systematic review included the treatment of all NET types with the exception of small-cell lung cancer (SCLC), because SCLC behaves as a very different clinical entity compared with other NET types, rarely demonstrates somatostatin receptors in a high concentration, and usually is treated under the lung cancer category.

METHODS

The evidence-based series guidelines developed by the Program in Evidence-Based Care (PEBC), CCO, use the methods of the Practice Guidelines Development Cycle (16). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by four members of the Radionuclide Therapy (RT) in NET Working Group and one methodologist of the PEBC. All data were audited by a second, and independent, person.

The systematic review is a convenient and up-to-date source of the best available evidence on RT for patients with malignant NETs. That evidence forms the basis of the recommendations developed by the RT Expert Panel and will be published when completed. A listing of the Expert Panel and Working Group members appears in Appendix 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

A literature search was performed using MEDLINE and EMBASE through the Ovid search engine from January 1, 1998, to November 4, 2010. The search strategies are reported in Appendices 2 and 3. The following resources were checked for existing systematic reviews and practice guidelines: the Cochrane Library (to Issue 10, 2010) and the Standards and Guidelines Evidence Inventory of Cancer Guidelines (referred to below as the Inventory) (17), which included guidelines identified in and/or published by the National Guideline Clearinghouse, the National Health and Medical Research Council (Australia), the New Zealand Guidelines Group, the Canadian Medical Association Infobase, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the European Neuroendocrine Tumour Society, among others. Over 1100 English-language cancer control guidelines and standards released from 2003 through June 2010 were available in the Inventory when it was checked on October 18, 2010.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion in this systematic review if they were:

1. Full text reports published from January 1, 1998, to November 4, 2010.
2. Clinical practice guidelines based on a systematic review, systematic reviews, randomized trials, prospective studies, or retrospective studies that reported on at least one clinical outcome.
3. Prospective studies that had ≥30 patients. This number was considered the minimum number of subjects on which results could be reported with enough certainty (e.g., narrow enough 95% confidence intervals [CI]) such that the data could be used in the formulation of recommendations.

4. Retrospective studies that had ≥100 patients. This number is greater than that chosen for prospective studies because retrospective studies have a greater potential for bias and thus can be more difficult to interpret.
5. Studies that included malignant NET patients who were inoperable or who had residual disease or metastases (patients could have been treated with prior systemic therapy).
6. Studies that reported or compared the effects of any of eight therapeutic radiopharmaceuticals listed in Table 1 on any of the following clinical outcomes: complete response (CR), partial response (PR), minor response (MR), stable disease (SD), duration of response (DR), PFS, OS, biochemical response, QOL, and toxicity.

Exclusion Criteria

Articles were excluded if they met any of the following criteria:

1. Were published in a language other than English.
2. Were non-systematic reviews, case reports, animal studies, letters, editorials or commentaries.
3. Recruited only patients with SCLC.
4. Did not report any outcomes after RT in which systemic therapy was immediately followed RT.

Synthesizing the Evidence

If possible, meta-analyses of each trial outcome would be considered and conducted. The subgroup data with a denominator less than 10 were not reported because a sample size <10 is considered a case report. Any data for which denominators were <30 should be considered carefully because they usually have extremely large 95% CIs and are unlikely to be statistically significant.

STATA 11.0 would be the statistical software for statistical calculation purposes and for producing figures. A two-sided significance level of $\alpha = 0.05$ was assumed.

RESULTS

Literature Search Results

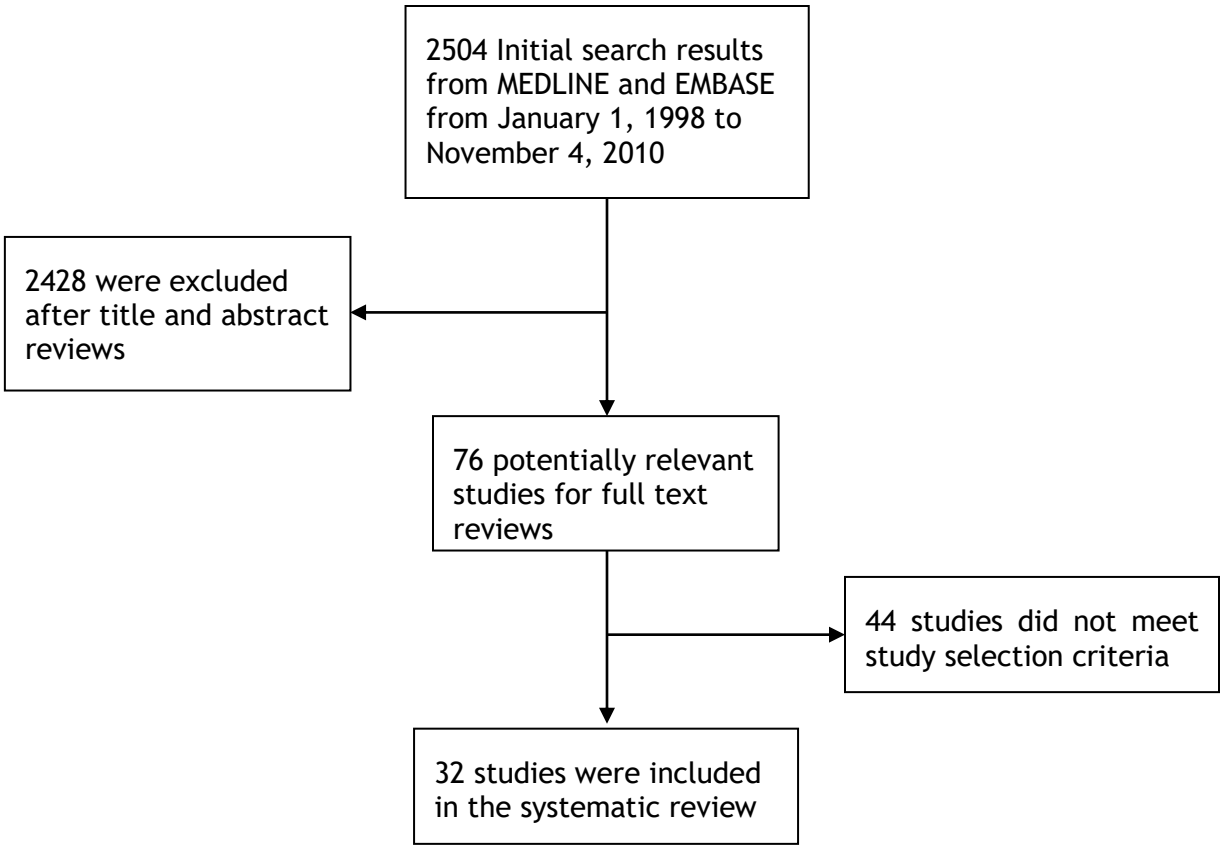
No existing systematic reviews or clinical practice guidelines based on a systematic review focusing on the topic of RT in malignant NET patients were found. Kwekkeboom et al developed a clinical guideline about PRRT in NET patients (18). However, they did not conduct a systematic review, and all the fully published studies in their guideline were retrieved by the MEDLINE and EMBASE searches in this systematic review.

Of 2504 citations identified from the electronic searches (Figure 1), 2428 articles were excluded after reviewing the titles and abstracts, and 44 were disqualified after reviewing the full texts, leaving 32 eligible articles (19-50). The reference lists of the included articles were hand searched, and no further eligible papers were found.

Several identified articles were multiple reports from the same or overlapping study populations and warranted further comment. The 2008 Kwekkeboom et al study (30) updated the 2003 (36) and 2005 studies (37) by the same group. Thus, only the 2008 Kwekkeboom et al study was summarized and analyzed in the tables and text.

The 2004 (25) and 2009 (31) Teunissen et al studies and the van Essen et al study (34) included a subset of patients from the 2008 Kwekkeboom et al study, but, because they reported new information and data beyond that study, these articles are summarized in the tables and text.

Figure 1. Flow of studies considered for this systematic review.



The 2010 Cwikla et al study analyzed 60 NET patients, 29 of whom had midgut NETs (33), and the 2009 Cwikla et al study recruited 34 midgut NET patients (39). The lead author of both papers was contacted and clarified that five midgut patients were recruited in the 2009 study after the 2010 paper was submitted for publication. Since the 2010 study included more patients than did the 2009 study (60 versus [vs.] 34, respectively) and the PR rate (18% vs. 19%; 29% vs. 33%, respectively) and SD rate (82% vs. 78%; 64% vs. 61%, respectively) for midgut NET patients at six and 24 month follow-up, respectively, were very similar, to avoid reporting duplicated information, only the 2010 Cwikla study (33) was summarized in the tables and text.

The 2005 Valkema et al study (38) included two groups of patients: 28 patients who were treated with ^{90}Y-DOTATOC and whose results were reported in the 2006 Valkema et al study (27), and 37 patients who were treated with ^{177}Lu-DOTATATE and whose results were completely included in the 2008 Kwekkeboom et al study (30). The 2002 Chinol et al study (35) recruited 86 NET patients and 25 patients with other tumours, and no clinical outcomes were reported separately for NET patients; in that same year, the Paganelli et al study (20), which was conducted by some of the same investigators at the same clinical centre as the Chinol et al study, recruited 87 NET patients. The 2001 Matthay et al (48) and 2004 DuBois et al (49) studies reported outcomes for 42 and 53 patients, respectively; all these patients were reported in the 1998 (40) and the 2007 (45) Matthay et al studies. The 2009 Gonias et al study (47) that analyzed 50 patients included all the patients in the 2006 Fitzgerald et al study (50). Therefore, the Valkema 2005, Chinol 2002, Matthay 2001, DuBois 2004, and Fitzgerald 2006 studies are not summarized in the following tables and text.

Finally, data were abstracted and summarized from 24 articles in this systematic review: 16 focused on PRRT (19-34), and eight focused on ^{131}I-MIBG treatment (40-47).

Study Design

Table 2 shows the study information, patient characteristics, and NET types for the 24 articles. There were no RCTs identified. Of the 16 articles in the PRRT category, one was a prospective comparative design, and the others were single-arm prospective designs (seven were phase II trials, and one was a phase I trial); the sample size ranged from 31 to 504 and the total sample size was 1179. Of the eight studies in the ^{131}I-MIBG therapy category, six were prospective single-arm studies (two were phase II trials and one was a phase I trial), one was a retrospective comparative study, and another was a retrospective single-arm study; the sample size ranged from 30 to 164, and the total sample size was 612.

In the PRRT category, all the patient tumours showed a higher or same uptake on octreoscan than did liver uptake before PRRT. The patient age ranged from 18 to 88 years old. The NET types of patients were various, but neuroblastoma was not found in these articles except for the 2008 Hubalewska-Dydejczyk et al study (29) that did not report NET types. All the patients had prior treatments such as surgery, chemotherapy, octreotide, external-beam radiation, biotherapy, or a combination of these therapies, except for those in the Hubalewska-Dydejczyk et al study, which had unclear pretreatment information (29). No patients had previous PRRT except for those in the 2010 van Essen et al study that investigated the additional two-cycle ^{177}Lu-DOTATATE treatment (34). Apart from two papers with unclear patient stages (19,22), eight articles included only stage IV patients (25,26,28-32,34), four articles included 85% or more patients with stage IV disease (23,24,27,33), and two articles included stage III or IV patients (20,21).

In the ^{131}I-MIBG therapy category, all the patients showed at least one positive lesion on the ^{123}I-MIBG or ^{131}I-MIBG scintigraphy. The patient age ranged from 0.5 to 70 years. Five studies recruited only stage III-IV neuroblastoma patients, with a median age of 2.0 to 6.6 years (40,41,43,45,46). The sixth study enrolled stage III-IV patients with various NETs, including 22 neuroblastomas, 10 pheochromocytomas, three paragangliomas, six medullary thyroid carcinomas, and four carcinoids (42). The seventh study enrolled stage IV midgut carcinoid patients (44), and the eighth recruited stage IV paraganglioma or pheochromocytoma patients (47). All of the patients had prior treatments such as surgery, chemotherapy, octreotide, external-beam radiation, biotherapy, or a combination of these therapies, except for the patients in the 2008 de Kraker et al study (46) who did not receive prior chemotherapy (some of them had only initial surgery) and five inoperable pheochromocytoma patients in the 2000 Castellani et al study (42) who did not receive any treatments before ^{131}I-MIBG therapy. No patients received prior ^{131}I-MIBG therapy in the eight studies, apart from one patient in the 1998 Matthay et al study (40).

Administered Dose and Treatment Schema

Table 3 outlines the details of administered dose and treatment schema for each therapeutic radiopharmaceutical in the 24 articles. In the PRRT category, no eligible studies investigated the effects of ^{111}In-octreotate or ^{177}Lu-octreotide in malignant NET patients. The minimum cumulative administered dose was 1.85 GBq with ^{90}Y-DOTALAN in the 2002 Virgolini et al study (22), and the maximum cumulative administered dose was 29.6 GBq with ^{177}Lu-DOTATATE in the 2008 Kwekkeboom et al study (30). In the 2010 van Essen et al study (34), patients in the 2008 Kwekkeboom study with an earlier benefit from pretreatment with ^{177}Lu-DOTATATE 18.5-29.6 GBq and who experienced progressive disease (PD) received another two-cycle ^{177}Lu-DOTATATE treatment; thus, the maximum cumulative administered dose was 44.4 GBq for some patients.

Table 2. Characteristics of included studies.

Study	Country	Design	N; Age (mean)	Patient characteristics at baseline	NET type
Peptide Receptor Radionuclide Therapy					
Waldherr 2001 (19)	Switzerland	Pros, phase II	41; 19-76 (median 51) y	All pts did not have antitumour treatment at least 2 y, 27 pts were postoperative, 15 pts had prior chemotherapy, 3 pts had chemoembolisation, 34 pts had PD, no stage information	14 EPTs, 8 intestinal, 7 bronchial, 8 UO, 1 paraganglioma, 1 carotid body tumour, 1 pheochromocytoma, 1 primitive
Paganelli 2002 (20)	Italy	Pros, phase II	87; ≥21 y	advanced NET, no details for pretreatments	50 GI, 14 MTC, 7 lung carcinoids, 16 others or UO
Valkema 2002 (21)	Netherlands	Pros, phase I	50*; 27-80 y	All pts were advanced stage without conventional treatment options, had PD or symptoms, 24 pts were postoperative, 8 pts had prior chemotherapy, 11 pts had prior radiotherapy.	4 foregut and 5 midgut carcinoids, 2 insulinomas, 1 glucagonoma, 2 gastrinomas, 1 VIPoma, 11 others, 2 pheochromocytomas, 1 glomus tumour, 5 MTC, 4 PTC, 1 FTC, 1 EPT
Virgolini 2002 (22)	Austria, UK, and Italy	Pros, phase II	39†; NR	All were malignant, no details for pretreatments, and no information of stages	34 carcinoids, 5 GEP-NETs
Waldherr 2002 (23)	Switzerland	Pros, phase II	39; ≥18 (55) y	All pts had PD, 31 pts had pretreatments, 15 pts were postoperative, 12 pts had prior chemotherapy, almost all were in stage IV, probably 1/39=3% in stage III	13 EPTs, 12 intestinal, 3 bronchial, 9 UO, 2 others
Nguyen 2004 (24)	France	Pros, comparative	32; 37-85 (63) y	31 pts were stage IV and 1 pt was stage III; 31 had prechemotherapy; 17 were postoperative	14 carcinoids, 7 gastrinomas, 5 GEP-NETs, 2 VIPomas, 2 UO, 1 glucagonoma, 1 insulinoma
Teunissen 2004 (25)	Netherlands	Pros	66‡; 30-78 (58) y	All pts had metastatic GEP tumours (stage IV), 22 pts were postoperative, 5 pts had prior chemotherapy, 17 pts had PD	26 carcinoids, 13 EPTs, 7 UO, 3 gastrinomas, 1 insulinoma
Forrer 2006 (26)	Switzerland	Pros	116; Mean 53 y	All pts had metastases (stage IV), no details for pretreatments, 94% pts had PD	45 EPTs, 28 UO, 24 intestinal, 10 bronchial, 9 others
Valkema 2006 (27)	Netherlands	Pros	58; 33-75 (54) y	All pts were advanced pts, 52 pts had liver metastases (stage IV), 32 pts were postoperative, 18 pts had prior chemotherapy, 9 had prior chemo-embolization, 47 pts had PD	5 foregut and 30 midgut carcinoids, 23 EPTs
Iten 2007 (28)	Switzerland	Pros, phase II	31; 24-77 (median 57) y	All pts were progressive stage IV , pretreatments included chemotherapy in 8 pts, radiation in 10 pts, radioiodine in 3 pts, and embolization in 3 pts	31 MTC
Hubalewska-Dydejczyk 2008 (29)	Poland	Pros	32; 37-75 (58) y	29 pts were disseminated (stage IV) and 3 pts were inoperable, no pretreatment information	NR
Kwekkeboom 2008 (30)	Netherlands	Pros	504§; 21-85 (59) y	All pts had metastases (stage IV), 153 pts were postoperative, 52 pts had prior chemotherapy, 133 pts had PD	188 carcinoids,72 nonfunctioning EPTs, 31 UO, 12 gastrinomas, 5 insulinomas, 2 VIPomas
Teunissen 2009 (31)	Netherlands	Pros	79‖; 20-83 (57) y	All pts had metastases (stage IV), 36 pts were postoperative, 6 pts had prior chemotherapy.	49 carcinoids, 15 EPTs, 8 UO, 3 Hürthle cell thyroid carcinomas, 1 gastrinoma, 1 insulinoma, 1 MTC, 1 paraganglioma
Bushnell 2010 (32)	Australia, Belgium, France, Sweden, UK, and USA	Pros, phase II	90; 18-88 (60) y	Metastatic carcinoid refractory to octreotide therapy (stage IV), 77 were postoperative, 28 pts had prior chemotherapy, 10 had radiotherapy.	90 carcinoids

Study	Country	Design	N; Age (mean)	Patient characteristics at baseline	NET type
Cwikla 2010 (33)	Poland	Pros, phase II	60; 23-73 (53) y	All pts were metastatic or progressive (48 in clinical stage IV, 8 in stage III, 4 in stage 2, but didn't give us the definition of clinical stages), 51 pts had liver involved, 30 pts had PD, 34 pts had prior chemotherapy, 30 pts were postoperative	25 foregut and 29 midgut carcinoids, 6 UO
van Essen 2010 (34)	Netherlands	Pros	33; 35-75 (median 57) y	All pts had metastases (stage IV), pts with an earlier benefit from pretreatment with ^{177}Lu-DOTATATE experienced PD	20 carcinoids (15 midgut, 3 bronchial, 1 gastric, 1 rectal), 8 EPTs, 5 UO
^{131}I-MIBG Therapy					
Matthay 1998 (40)	USA	Pros, phase I	30; 0.5-32 (median 4.2) y	All pts had prior chemotherapy and were refractory to conventional therapy, 28 pts were postoperative, 1 pt had prior ^{131}I-MIBG treatment 6 y ago, 24 pts were in stage IV and 6 were in stage III	30 neuroblastomas
Garaventa 1999 (41)	Italy	Pros	43, 1-17 (median 2) y	13 stage III pts with residual tumour and 30 stage IV pts positive at the ^{123}I- or ^{131}I-MIBG scintigraphy, without CR at end of first-line therapy	43 neuroblastomas
Castellani 2000 (42)	Italy	Pros	45; 2-70 y	Stage III-IV pts with residual, inoperable, or progressive disease, most pts had prior chemotherapy, 5 inoperable pheochromocytoma pts did not get any treatment before ^{131}I-MIBG	22 neuroblastomas, 10 pheochromocytomas, 3 paragangliomas, 6 MTC, 4 carinoids
Garaventa 2003 (43)	Italy	Retro	119; 1.5-13.5 (median 4.5) y	27 stage III pts and 92 stage IV pts, either as part of first-line therapy or as salvage therapy for resistant or recurrent disease, no pretreatment detail	119 neuroblastomas
Sywak 2004 (44)	Canada	Retro, comparative	117; 57-66 (60) y	Progressive metastatic pts (stage IV) with standard therapies. Except ^{131}I-MIBG, 2 groups had similar proportion of pts with surgery, chemotherapy, external beam radiotherapy, interferon, and octreotide	117 midgut carcinoids
Matthay 2007 (45)	USA	Pros, phase II	164; 1.8-30.2 (median 6.6) y	Refractory or relapsed or PD high-risk stage III-IV pts, 1-13 prior regimens for all pts, 90% pts had prior radiation and surgery (no information about prior chemotherapy)	164 neuroblastomas
de Kraker 2008 (46)	Netherlands	Pros	44; 1.0-15.4 (median 2.6) y	Just diagnosed stage IV pts without chemotherapy before, some pts had initial surgery for neuroblastomas	44 neuroblastomas
Gonias 2009 (47)	USA	Pros, phase II	50¶; 10-64 (median 43) y	All pts were metastatic stage IV, 44 pts were postoperative, 16 pts had prior radiation and 15 pts had prior chemotherapy	34 paragangliomas, 15 pheochromocytomas

Abbreviations: N = sample size of patients at the baseline, NET = neuroendocrine tumour, Pros = prospective, y = years, pts = patients, PD = progressive disease, EPT = endocrine pancreatic tumour, UO = unknown origin, GI = gastrointestinal, MTC = medullary thyroid carcinoma, PTC = papillary thyroid carcinomas, FTC = follicular thyroid carcinoma, UK = United Kingdom, NR = not reported, GEP = gastroenteropancreatic, VIPoma = vasoactive intestinal peptide-secreting tumour, USA = United States, MIBG = metaiodobenzylguanidine, CR = complete response, Retro = retrospective.

*Only 40 patients were analyzed, and their NET types were specified.
†The Multicenter Analysis of a Universal Receptor Imaging and Treatment Initiative (MAURITIUS) trial included 154 patients, but only 39 were NET patients.
‡There were 66 patients at baseline, and 50 were analyzed; these patients were the first 50 local resident patients in the 2008 Kwekkeboom study.
§There were 504 patients at baseline, and they were analyzed for toxicity, but patient characteristics and treatment effects were available for 310 patients.
‖The endocrine functions of 79 patients who were local residents from 504 patients in the 2008 Kwekkeboom study were analyzed.
¶There were 50 patients at baseline, and data from 49 patients were available.

Table 3. Administered dose and treatment schema.

Study	Dose/cycle	Frequency	Cycle times; accumulated dose
^{111}In-DTPAOC			
Valkema 2002 (21)	2 GBq (3 pts), 6-7 GBq (40 pts), 10-11 GBq (7 pts)	Several mo (3 pts), at least 2 weeks (47 pts)	NR for 3 pts, 8-22 cycles for 47 pts; 20-160 GBq
Nguyen 2004 (24*)	7 GBq	1 mo	2 cycles (1 pt), 3 cycles (11 pts), 6 cycles (3 pts); 13.1-42.8 GBq
	3.7 GBq for pts < 50 kg, 5.6 GBq for pts 50-70 kg, 7.4 GBq for pts >70 kg	1 mo	2 cycles (1 pt), 3 cycles (4 pts)
^{90}Y-DOTATOC			
Waldherr 2001 (19)	0.925-2.035 GBq/m^2	6 weeks	4 cycles; 6 GBq/m^2
Waldherr 2002 (23)	1.85 GBq/m^2	6 weeks	4 cycles; 7.4 GBq/m^2
Paganelli 2002 (20)	2.96-5.55 GBq	At least 6-8 weeks	Median 4 cycles; 7.4-20.2 GBq
Forrer 2006 (26)	1.50-1.85 GBq/m^2 (80 pts), 3.7 GBq/m^2 (36 pts)	6 weeks (80 pts), 8 weeks (36 pts)	4 cycles (80 pts), 2 cycles (36 pts); 6.0-7.4 GBq/m^2
Valkema 2006 (27)	0.925 GBq/m^2	6-9 weeks	Up to 4 cycles; 7.2-14.9 GBq/m^2
Iten 2007 (28)	3.7 GBq/m^2	6 weeks	Up to 5 cycles; 1.7-29.6 (median 12.6) GBq
Bushnell 2010 (32)	4.4 GBq	6-9 weeks	1 cycle (9 pts), 2 cycles (7 pts), 3 cycles (73 pts) 5 cycles (1 pt: 1 cycle of 4.4 GBq and 4 cycles of 2.2 GBq); 4.3-13.2 GBq
^{90}Y-DOTALAN			
Virgolini 2002 (22)	Initial 1 GBq	4 weeks	1-7 cycles (34 carcinoid pts), 3-4 cycles (5 GEP-NET pts); 1.85-8.58 GBq (34 carcinoid pts), 2.78-3.7 GBq (5 GEP-NET pts)
^{90}Y-DOTATATE			
Hubalewska-Dydejczyk 2008 (29)	NR	4-9 weeks	3-5 cycles; 7.4 GBq/m^2
Cwikla 2010 (33)	NR	6-9 weeks	2 cycles (11 pts), 3 cycles (38 pts), 4 cycles (12 pts); 4.1-15.2/16.2 (mean 11.2) GBq†
^{177}Lu-DOTATATE			
Teunissen 2004 (25)	NR	6-9 weeks	3-4 cycles; 22.2-29.6 GBq
Kwekkeboom 2008 (30)	3.7 GBq (7 pts), 5.6 GBq (16 pts), 7.4 GBq (481 pts)	6-10 weeks	Up to 4 cycles; Up to 27.8-29.6 GBq
Teunissen 2009 (31)	NR	6-9 weeks	3-4 cycles; 22.2-29.6 GBq
van Essen 2010 (34)	3.7 GBq (1 pt), 7.4 GBq (32 pts)	6-10 weeks‡	1 cycle (4 pts), 2 cycles (29 pts); 3.7 GBq (1 pt), 7.4 GBq (3 pts), 14.8 GBq (29 pts)
^{131}I-MIBG Therapy			
Matthay 1998 (40)	3.33-29.6 GBq: 0.11-0.22 GBq/kg (3 pts), 0.33 GBq/kg (6 pts), 0.44 GBq/kg (6 pts), 0.56GBq/kg (6 pts), 0.67 GBq/kg (9 pts)	4 weeks	1 cycle (20 pts), 2 cycles (6 pts), 3 cycles (3 pts), 4 cycles (1 pt); NR

Garaventa 1999 (41)	2.5-3.7 GBq for pts <15 kg, 3.7-4.7 GBq for pts 15-20 kg, 5.5 GBq for pts >20 kg	4-6 weeks	1 cycle (6 pts), 2 cycles (15 pts), 3 cycles (14 pts), 4 cycles (7 pts), 5 cycles (1 pts); NR
Castellani 2000 (42)	2.7-5.5 GBq for children, 3.7-7.4 GBq for adults	At least 4 weeks	1-10 cycles; NR
Garaventa 2003 (43)	2.5-3.7 GBq for pts <15 kg, 3.7-4.7 GBq for pts 15-20 kg, 5.5 GBq for pts >20 kg	4-6 weeks	1-5 (median 2) cycles; NR
Sywak 2004 (44)	Median 6.75 GBq	NR	Mean 2.8 cycles; Median 18.9 GBq
Matthay 2007 (45)	0.67 GBq/kg (132 pts), 0.44 GBq/kg (16 pts), 0.32-0.59 GBq/kg (16 pts)	6 weeks	1 cycle (129 pts), multiple cycles (35 pts); NR
de Kraker 2008 (46)	7.4 GBq for cycle 1; 3.7-5.6 GBq for cycle 2	4 weeks	1 cycle (6 pts), 2 cycles (39 pts); 7.4 GBq for 6 pts, 13-35 GBq for 39 pts
Gonias 2009 (47)	18.2-42.9 GBq	NR	1 cycle (35 pts), 2-3 cycles (14 pts); 18.2-118.1 GBq

Abbreviations: GBq = Gigabecquerel, pts = patients, mo = month, GEP = gastroenteropancreatic, NET = neuroendocrine tumour, kg = kilogram, NR = not reported.

*The second row of this study shows 5 patients treated with ^{131}I-MIBG.
†The original author stated, "patients were treated up to a cumulative activity of **15.2 GBq,**" on page 788, but on page 789, "A total of 180 therapies were given with a mean administered activity of 11.2 GBq (range 4.1-**16.2 GBq**)."
‡This information was copied from Kwekkeboom et al (30), since this study was a subgroup ongoing study from Kwekkeboom et al (30) at the same clinical centre.

In the ^{131}I-MIBG therapy category, only three of eight studies reported the cumulative administered dose data (44,46,47): the minimum cumulative dose was 7.4 GBq, in the 2008 de Kraker et al study (46), and the maximum cumulative dose was 118.1 GBq, in the 2009 Gonias et al study (47).

Study Quality

The 24 included studies were assessed for quality (Table 4), according to the Newcastle-Ottawa Scale (51) used in non-randomized studies (NRS) method group workshops of the Cochrane Collaboration to illustrate issues in data extraction from primary NRS (52). Overall, the quality of these studies was poor to moderate. Twenty-two single-arm articles prospectively included various advanced NET patients, and the administered doses and treatment schemas of RT were recorded clearly. One prospective comparative study was conducted in one clinical centre (24), and one retrospective comparative study drew patients in the control and intervention groups from two different centres (44). Except for the 2010 van Essen et al study (34), where the investigators stated that they were unclear if the additional ^{177}Lu-DOTATATE would work in progressive patients who received benefit from previous ^{177}Lu-DOTATATE treatment, the studies seemed to be designed based on the previous case reports or very small sample size studies that showed therapeutic radiopharmaceuticals resulting in some response in NET patients. Only the 2004 Nguyen et al study specified that the outcome assessment of tumour responses was blinded with respect to treatment (24). This present systematic review arbitrarily considered the follow-up time to be adequate if the upper limit of the follow-up range in a study was ≥24 months; based on this rule, 18 articles had sufficient follow-up time (19-22,24,27,28,30,32-34,40-45,47). All but the 2004 Teunissen et al study (25) analyzed ≥80% of patients for at least one clinical outcome.

Table 4. Assessment of study quality by the Newcastle-Ottawa Scale.*

Study	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for age with or without other factors	Blinded assessment of outcome†	Adequate follow-up (time) ‡	Adequate follow-up (patients)§
PRRT								
Waldherr 2001 (19)	Yes	NA	Yes	No	NA	Unclear	Yes‖	Yes
Paganelli 2002 (20)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Valkema 2002 (21)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Virgolini 2002 (22)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Waldherr 2002 (23)	Yes	NA	Yes	No	NA	Unclear	No	Yes
Nguyen 2004 (24)¶	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Teunissen 2004 (25)	Yes	NA	Yes	No	NA	Unclear	No	No
Forrer 2006 (26)	Yes	NA	Yes	No	NA	Unclear	No	Yes
Valkema 2006 (27)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Iten 2007 (28)	Yes	NA	Yes	No	NA	Yes#	Yes	Yes
Hubalewska-Dydejczyk 2008 (29)	Yes	NA	Yes	No	NA	Unclear	Unclear	Yes
Kwekkeboom 2008 (30)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes**
Teunissen 2009 (31)	Yes	NA	Yes	No	NA	Yes#	No	Yes
Bushnell 2010 (32)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Cwikla 2010 (33)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
van Essen 2010 (34)	Yes	NA	Yes	Yes	NA	Unclear	Yes	Yes
^{131}I-MIBG Therapy								
Matthay 1998 (40)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Garaventa 1999 (41)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Castellani 2000 (42)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
Garaventa 2003 (43)	Yes	NA	Yes	No	NA	No	Yes	Yes
Sywak 2004 (44)	Unclear	No	Yes	No	Yes	No	Yes	Yes
Matthay 2007 (45)	Yes	NA	Yes	No	NA	Unclear	Yes	Yes
de Kraker 2008 (46)	Yes	NA	Yes	No	NA	Unclear	NA	Yes
Gonias 2009 (47)	Yes	NA	Yes	No	NA	No	Yes	Yes

Abbreviations: PRRT = peptide receptor radionuclide therapy, NA = not applicable.

*The Newcastle-Ottawa Scale includes three domains: selection, comparability, and outcome. Yes = high quality; No = low quality.
†The outcome assessors were blinded to the intervention/exposure.
‡Since several included studies reported renal toxicity or myelodysplastic syndrome at 24 months after PRRT, the upper range of follow-up time of at least 24 months was arbitrarily determined as adequate.
§Adequacy of follow-up was arbitrarily defined as ≥ 80% of patients being analyzed for at least one of clinical outcomes.
‖Although the median follow-up was 15 months, the authors reported overall survival rate at 24 months; so "Yes" was given.
¶In this study, 15 patients were treated by ^{111}In-DTPAOC, 5 patients were treated by ^{131}I-MIBG, and 12 patients were not treated.
#The assessment of biochemical tests was treated as an objective evaluation; so it was blinded by nature.
**Three hundred ten (62%) patients were analyzed for efficacy, but 504 (100%) patients were analyzed for toxicity.

Outcomes

Meta-analyses of the trial results for tumour response rates on imaging and/or survival time/rates were not feasible. The various clinical centres differed in RT interventions, doses and treatment schema for the same intervention, patient characteristics, NET types, tumour status at baseline, and criteria for evaluating tumour response, making meaningful results from pooling impossible. Meta-analyses of outcomes for biochemical response, QOL, and/or toxicity were also not feasible because of the differences in outcome assessment measurement and timing.

Survival Time/Rate

Tables 5a and 5b summarize the outcomes of survival for PRRT and ^{131}I-MIBG therapy in various types of malignant NET patients, respectively.

1. Peptide Receptor Radionuclide Therapy

Eight articles reported survival outcomes (19,21,24,27,30,32-34). In five of the six articles, the median OS time after PRRT ranged from 16 months for patients with progressive stage IV medullary thyroid cancer treated with ^{90}Y-DOTAOC in the 2007 Iten et al study (28) to 46 months for patients at stage IV in various gastroenteropancreatic (GEP) NETs treated with ^{177}Lu-DOTATATE in the 2008 Kwekkeboom et al study (30). The sixth article showed the median OS time to be 15 months for patients who had had an earlier benefit from pretreatment with ^{177}Lu-DOTATATE in the 2008 Kwekkeboom et al study and whose disease progressed again and received additional ^{177}Lu-DOTATATE (34). Three studies were conducted in the same clinical centre at different time periods, and the tumour response was assessed by the same criteria (21,27,30): the median OS and PFS time was 37 and 14 months, respectively, for various stage III-IV GEP-NET patients treated with ^{90}Y-DOTATOC at five years (27), and 46 and 33 months, respectively, for various stage IV GEP-NET patients treated with ^{177}Lu-DOTATATE at up to four years (30); the overall response rate was 18% (CI, 6% to 30%) for various progressive stage III-IV NET patients treated with ^{111}In-DTPAOC, 21% (CI, 11% to 31%) from ^{90}Y-DOTATOC treatment, and 46% (CI, 40% to 52%) from ^{177}Lu-DOTATATE treatment.

In the 2004 Nguyen et al study, the intervention group (14 patients treated with ^{111}In-DTPAOC and five patients treated with ^{131}I-MIBG) had statistically significantly higher OS and PFS rates than did the control group (12 patients without treatment) at 15 months but not at the end of the follow-up period (24).

2. ^{131}I-MIBG therapy

Five studies reported survival outcomes (40,41,44,45,47). In three studies focusing on stage III-IV neuroblastoma patients, the median OS rate was six months in the 1998 Matthay et al study (40), the OS rate was 49% at one year and 29% at two years in the 2007 Matthay et al study (45), while the PFS rate was 92% (95% CI, 78% to 100%) for stage III patients and 40% (CI, 24% to 56%) for stage IV patients at five years in the 1999 Garaventa et al study (41). Patients in the 1998 and 2007 Matthay et al studies were either refractory to conventional therapy or relapsed, but all the patients in the 1999 Garaventa et al study did not have CR at the end of first-line therapy, which may explain why these patients had a high PFS rate at five years.

For stage IV paraganglioma or pheochromocytoma patients with an accumulated dose of 18.2-118.1 GBq, the OS rate was 64% (CI, 46% to 82%) and the PFS rate was 47% (CI, 31% to 63%) at five years in the 2009 Gonias et al study (47).

In the lone comparative study (^{131}I-MIBG treatment versus no treatment) (44), the OS rates did not differ between the intervention and control groups (63% vs. 47%, p=0.10) for patients with progressive, stage IV midgut carcinoid.

Table 5a. Clinical outcomes of response on imaging and survival time/rate for peptide receptor radionuclide therapy.

Study	NET type	Tumour status/stage at baseline	N for analysis (%)	Response on imaging						DR (mo)	F-up time (mo)	OS time/rate [CI]	PFS time/rate
				CR rate	PR rate	MR rate	OR rate [95% CI]	SD rate	PD rate				
^{111}In-DTPAOC													
Valkema 2002 (21)*	**Various**	Progressive/ symptomatic, stage III-IV	40 (80%)	0%	3%	15%	18% [6 to 30]	35%	NR	NR	1-55 (median 13)	NR	NR
Nguyen 2004 (24)†	**Various (Intervention)**	Progressive/ symptomatic, stage III-IV (97% in stage IV)	19 (95%)	0%	5%	0%	5% [0 to 15]	84%	11%	Mean 16	5-57 (mean 27)	In favour of intervention group at 15 mo, but no difference at the end of F-up	In favour of intervention group at 15 mo
	Various (Control)		12 (100%)	0%	0%	0%	0%	42%	58%	NA	2-17 (mean 10)		
^{90}Y-DOTATOC													
Waldherr 2001 (19)‡	**Various**	Mixed§, unclear stage	41 (100%)	2%	22%	0%	24% [11 to 37]	61%	15%	Median DR >26	2-26 (median 15)	76% [60 to 92] at 24 mo	NR
	EPT		14 (100%)	0%	36%	0%	36% [11 to 61]	50%	14%			NR	NR
Waldherr 2002 (23)‡	**Various**	Progressive, stage III-IV (97% in stage IV)	39 (100%)	5%	18%	0%	23% [10 to 36]	69%	8%	NR	2-12 (median 6)	NR	NR
	EPT		13 (100%)	8%	31%	0%	39% [12 to 66]	46%	15%				
	Intestinal		12 (100%)	0%	8%	0%	8% [0 to 23]	92%	0%				
Paganelli 2002 (20)*	**Various**	Mixed§, stage III-IV	87 (100%)	5%	23%	NR	CR + PR = 28% [19 to 37]	49%	20%	2-27 (mean 14)	At least 2-27 (mean 14)	NR	NR
		Progressive, stage III-IV	66 (100%)	5%	21%	NR	CR + PR = 26% [15 to 37]	48%	23%				
Forrer 2006 (26)‡	**Various**	94% pts were progressive, stage IV	116 (100%)	4%	22%	0%	26% [18 to 34]	62%	11%	NR	3	NR	NR
Valkema 2006 (27)*	**Various GEP-NET**	Mixed§, stage III-IV (90% in stage IV)	58 (100%)	0%	9%	12%	21% [11 to 31]	50%	24%	NR	About 60§	19-54 (median 37) mo	9-20 (median 14) mo
		Progressive, stage III-IV	47 (100%)	0%	11%	11%	22% [10 to 34]	45%	28%			Around 21% at 60 mo‖	NR
Iten 2007 (28)	**MTC**	Progressive, stage IV	31 (100%)	NA						NA	1.4-107 (median 12.1)	1-107 (median 16) mo	NR
Bushnell 2010 (32)*¶	**Various carcinoid**	Progressive, stage IV	90 (100%)	0%	4%	0%	4% [0 to 8]	70%	12%	10	20-33	Median 27 mo	Median 16 mo
^{90}Y-DOTALAN													
Virgolini 2002 (22)‡	**Carcinoid**	Unclear	34 (100%)	NR	NR	NR	18% [5 to 31]	44%	38%	Unclear	Over 36	NR	NR
^{90}Y-DOTATATE													
H-D 2008 (29)#	**Various**	Stage IV	32 (100%)	0%	44%	0%	44% [27 to 61]	30%	26%	Mean 18	At least mean 18	NR	NR
Cwikla 2010 (33)**	**Various GEP - NET at 6 mo**	Progressive, 85% pts in stage IV	57 (95%)	0%	23%	0%	23% [12 to 34]	77%	0%	NR	Up to 36	Median 22 (20 to 27) mo; median 10 mo for DP pts versus median 24 mo for SD or PR pts (p-value < 0.05)	Median 17 (16 to 21) mo; median 5 mo for DP pts versus median
	At 12 mo		43 (72%)	0%	35%	0%	35% [21 to 49]	56%	9%				
	At 24 mo		22 (37%)	0%	23%	0%	23% [5 to 41]	50%	27%				
	Foregut at 6 mo		25 (100%)	0%	24%	0%	24% [7 to 41]	76%	0%				

	At 12 mo		14 (56%)	0%	21%	0%	21% [0 to 42]	64%	14%				20 mo for SD or PR pts (p<0.05)
	Midgut at 6 mo		28 (97%)	0%		0%	18% [4 to 32]	82%	0%				
	At 12 mo		25 (86%)	0%	40%	0%	40% [21 to 59]	52%	8%				
	At 24 mo		14 (48%)	0%	29%	0%	29% [5 to 53]	64%	7%				
^{177}Lu-DOTATATE													
Kwekkeboom 2008 (30)*	**Various GEP-NET**	Mixed§¶, stage IV	310 (62%)	2%††	28%	16%	46% [40 to 52]	35%	20%	NR	Up to 48 (median 19)	Median 46 mo, pts with PD have significantly shorter survival	Median 33 mo
	Carcinoid		188	1%	22%	17%	40% [33 to 47]	42%	20%				
	Nonfunctioning EPT		72	6%	36%	18%	60% [49 to 71]	26%	14%				
	UO		31	0%	32%	10%	42% [25 to 59]	23%	36%				
	Gastrinoma		12	0%	42%	33%	75% [51 to 100]	17%	8%				
van Essen 2010 (34)*	**Various GEP-NET**	Progressive, stage IV	33 (100%)	0%	6%	18%	24% [9 to 39]	24%	52%‡‡	Median 17	1-40 (median 16)	Median 15 mo; pts with PD have significantly shorter survival	NR
	Carcinoid		20 (100%)	0%	NR	NR	NR	NR	48%	Median 20			

Abbreviations: NET = neuroendocrine tumour, N = number of patients, CR = complete response, PR = partial response, MR = minor response (defined as reduction in tumour size between 25% and 50%), OR = overall response (defined as sum of CR, PR, and MR rates), CI = confidence interval, SD = stable disease, PD = progressive disease, DR = duration of response (among patients with CR, PR, MR, or SD), mo = months, F-up = follow-up, OS = overall survival, PFS = progression-free survival, EPT = endocrine pancreatic tumour, GEP = gastroenteropancreatic, MTC = medullary thyroid cancer, H-D = Hubalewska-Dydejczyk, UO = unknown origin, pts = patients, NR = not reported, NA = not applicable.

*Tumour response was assessed by the Southwest Oncology Group criteria. The definition for CR: Complete disappearance of all measurable and evaluable disease; PR: Sum of products of all lesions decreased by ≥50% for at least 3-6 weeks, no new lesions and no progression of evaluable lesions; SD: Sum of products of lesions decreased by <50% or increased by <50% or 10 cm^2 for at least 3-6 weeks; PD: 50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over the smallest sum observed; clear worsening of any evaluable disease; appearance of a new lesion.

†Tumour response was assessed by the World Health Organization (WHO) standard criteria, but the original investigators defined PD as an increase in tumour diameter of >25% instead of >50% for WHO criteria. The intervention group included 14 pts treated with ^{111}In-DTPAOC and five patients treated with ^{131}I-MIBG; one patient had PR shown in their Table 3, but was described as MR on page 1665. In the control group, one patient required chemotherapy alone, one needed chemotherapy combined with external radiotherapy, two needed radiotherapy alone, and one needed chemoembolization as rescue therapy later.

‡Tumour response was assessed by WHO standard criteria. The definition for CR: Disappearance of all known disease determined by two observations not less than 4 weeks part; PR: Sum of products of all lesions decreased by >50% for at least 4 weeks, no new lesions, no progression of any lesions; SD: Sum of products of lesions decreased by <50% or increased by <25% in the size of one or more lesions; PD: A single lesion increased by >25% (over the smallest measurement achieved for the single lesion) or the appearance of new lesions.

§Some patients were progressive and others were stable.

‖Measured from Figure 2 in the original paper.

¶Four pts died on study, 8 pts were lost to f-up; Intent-to-treat analysis was used.

#H-D = Hubalewska-Dydejczyk; tumour response criteria was not specified.

**Tumour response was assessed by the Response Evaluation Criteria in Solid Tumours. The definition for CR: Complete disappearance of all target and non-target lesions for at least 4 weeks; PR: Sum of the maximum diameter of all lesions decreased by >30%, no new lesions, no progression of disease; SD: Sum of the maximum diameter of lesions decreased by <30% or increased by <20% for a defined period; PD: Sum of the maximum diameter of lesions increased by >20% over the smallest achieved sum of maximum diameter, or a new lesion appeared.

††CR was only called if both conventional imaging and the octreoscan had normalized.

‡‡Two pts with radiological SD had clear clinical signs of DP and were classified as having PD.

Table 5b. Clinical outcomes of response on imaging and survival time/rate for ^{131}I-MIBG Therapy.

Study	NET type	Tumour status/stage at baseline	N for analysis (%)	Response on imaging						DR (mo)	Follow-up time (mo)	OS time/rate [CI]	PFS Rate [CI]
				CR rate	PR rate	MR rate	OR rate [95% CI]^	SD rate	PD rate				
Matthay 1998 (40)*	Neuroblastoma	Refractory and relapsed, stage III-IV (80% in stage IV)	30 (100%)	3%	33%	10%	46% [28 to 64]	20%	33%	2-67	NR	1-51 (median 6) mo	NR
Garaventa 1999 (41)†	Neuroblastoma	Stage III-IV	43 (100%)	2%	28%	2%	32% [18 to 46]	56%	12%	NR	9-153 (median 36)	NR	NR
		Stage III	13 (100%)	0%	15%	8%	23% [0 to 46]	69%	8%				92% [78 to 100] at 5 y
		Stage IV	30 (100%)	3%	33%	0%	36% [19 to 53]	50%	13%				40% [24 to 56] at 5 y
Castellani 2000 (42)‡	Various	Stage III-IV	41 (91%)	2%	24%	0%	26% [13 to 39]	51%	17%	3-92	3-92	NR	NR
	Neuroblastoma	Stage III-IV	21 (95%)	0%	24%	0%	24% [6 to 42]	57%	19%	3-92	3-92		
Sywak 2004 (44)	Midgut carcinoid (Intervention)	Progressive, stage IV	58 (100%)	NR						NR	59-101 (mean 79)	63% (47 to 75) at 5 y	NR
	Midgut carcinoid (Control)	Progressive, stage IV	59 (100%)	NR						NR	43-78 (mean 60)	47% [34 to 59] at 5 y (no statistic difference)	NR
Matthay 2007 (45)†	Neuroblastoma	Refractory or relapsed or PD, stage III-IV	163 (99%)	8%	28%	3%	39% [32 to 46]	34%	27%	Median 6	0.5-95.6 (median 9.4)	49% at 1 y, 29% at 2 y	18% at 1 y§
		ST ± B/BM with HCT	72 (99%)	7%	25%	3%	35% [24 to 46]	39%	26%				
		B/BM with HCT	55 (100%)	15%	35%	2%	52% [39 to 65]	27%	22%				
		ST ± B/BM without HCT	31 (100%)	0%	29%	6%	35% [18 to 52]	29%	35%				
de Kraker 2008 (46)†‖	Neuroblastoma	Stage IV	41 (93%)	2%	63%	10%	75% [62 to 88]	12%	10%	NA	NA	NA	NA
Gonias 2009 (47)¶	Paragangliomas, pheochromo-cytomas	Stage IV	45 (90%)	9%	18%	0%	27% [14 to 40]	53%	20%	NR	1-180 (median 24)	64% [46 to 82] at 5 y	47% [31 to 63] at 5 y§

Abbreviations: NET = neuroendocrine tumour, N = number of patients, CR = complete response, PR = partial response, MR = mixed response (defined as some lesions had PR and some lesions had stable disease), OR = overall response (defined as sum of CR, PR, and MR rates), CI = confidence internal, SD = stable disease, PD = progressive disease, DR = duration of response (among patients with CR, PR, MR, or SD), mo = months, OS = overall survival, PFS = progression-free survival, ST = soft tissue, B = bones, BM = bone marrow, HCT = hematopoietic cell transplant, NR = not reported, NA = not applicable.

*Tumour response was assessed by the International Neuroblastoma Response Criteria (Brodeur 1988 version). The definition for CR: No tumour for primary lesion and metastases, and homovanillic acid (HVA)/vanillylmandelic acid (VMA) are normal; PR: No new lesions, all lesions reduced ≥50%, 0-1 bone marrow samples with tumour, and HVA/VMA decreased ≥50%; SD: No new lesions, <50% reduction but <25% increase in any existing lesion; MR: Between PR and SD; PD: Any new lesion, increase of any measurable lesion by >25%, previous negative marrow positive for tumour.

†Tumour response was assessed by the International Neuroblastoma Response Criteria (Brodeur 1993 version). The definition for CR: No tumour for primary lesion and metastases, and catecholamines are normal; PR: No new lesions, all lesions reduced >50%, no more than one positive bone marrow site allowed; SD: No new lesions, <50% reduction but <25% increase in any existing lesion; MR: Between PR and SD; PD: Any new lesion, increase of any measurable lesion by >25%, previous negative marrow positive for tumour.

‡Tumour response was assessed by the International Union Against Cancer. The definition for CR: Complete disappearance of all known disease for at least one month; PR: ≥50% decrease in sum of products of two largest perpendicular diameters of all tumour masses for at least one month; SD: <50% decrease or <25% increase in known, measurable lesions; PD: ≥25% increase in any tumour lesion or new lesion.

§¶It shows event-free survival rate.

‖Response on imaging was just showed after cycle 2 of MIBG treatment; after MIBG treatment, pts got surgery, chemotherapy, etc. treatment, so the survival data could not reflect the effect of MIBG and were not showed in this table.

¶Response after second treatment was showed here; tumour response was assessed by their own criteria: CR = all lesions visible disappearance on CT/MRI scan; PR = the sum of the longest diameter of index lesions decreased ≥30%; SD = the sum was between PR and PD; PD = the sum of the longest diameter of targeted lesions increased ≥20%.

Response on Imaging

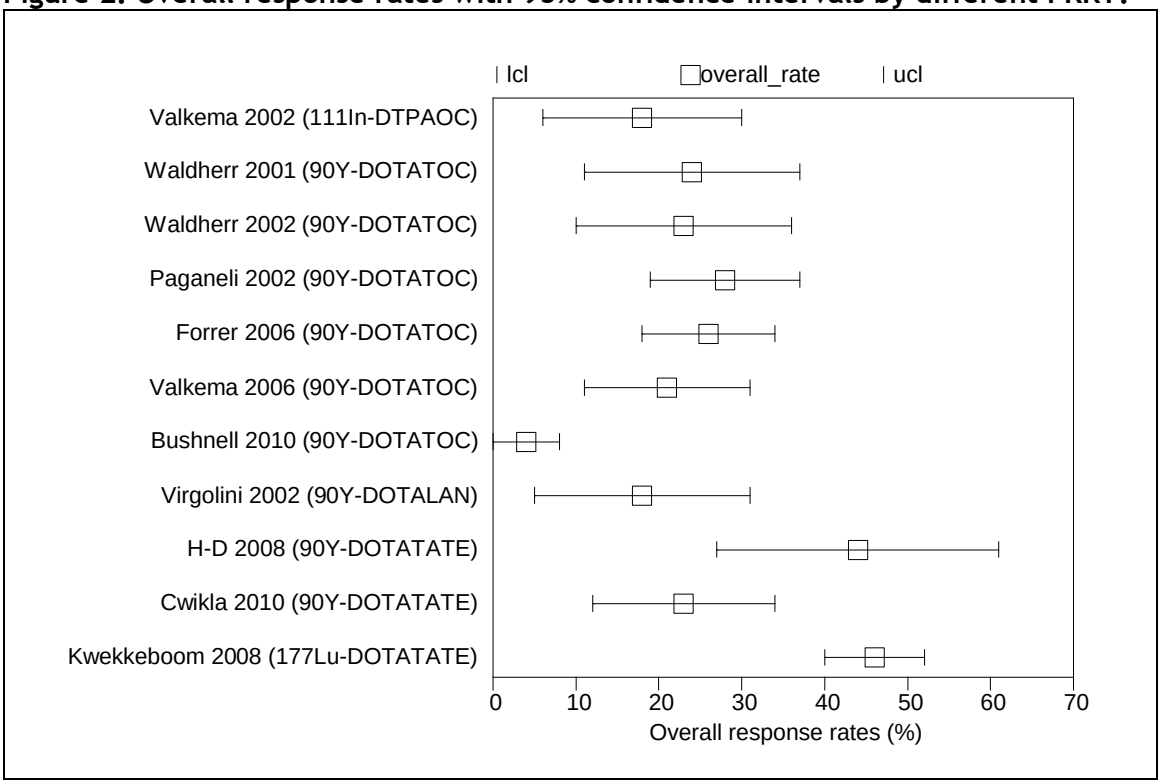
Tables 5a and 5b summarize the outcomes of tumour response on imaging for PRRT and ^{131}I-MIBG therapy in various types of malignant NET patients, respectively.

1. Peptide Receptor Radionuclide Therapy

Three different criteria were used to evaluate tumour response: the Southwest Oncology Group (SWOG) criteria, the World Health Organization (WHO) standard criteria, and the Response Evaluation Criteria in Solid Tumours (RECIST). The different criteria had different definitions, especially for PR, SD, and PD (53), making the comparison among studies difficult. For example, the definition of PR was the sum of the maximum diameter of all lesions decreased by ≥30% using RECIST criteria, the sum of products of all lesions decreased by ≥50% for at least three to six weeks using SWOG criteria, and the sum of products of all lesions decreased by ≥50% for at least four weeks using WHO criteria (see notes under Table 5a). Some studies, such as the 2008 Kwekkeboom et al study (30), reported the MR rate as a reduction in tumour size of between 25% and 50%, because NETs grow slowly in general. For the above reasons, the sum of the CR, PR, and MR rate is thought to be a reasonable tumour response item and is called overall response rate in this systematic review.

For ^{111}In-DTPAOC, the overall response rate was 18% (CI, 6% to 30%) for various progressive stage III-IV NETs in the 2002 Valkema et al study (21) and 5% (CI, 0 - 15%) in the intervention group of 19 patients (five patients received ^{131}I-MIBG therapy) in the 2004 Nguyen et al study (24). For ^{90}Y-DOTATOC, the overall response rate ranged from 24% (CI, 11% to 37%) to 28% (CI, 19% to 37%) for various mixed-status stage III-IV NETs (19,20,26); the overall response rate was 26% (CI, 15% to 37%) and 23% (CI, 10% to 36%) for various progressive stage III-IV NETs in two studies (20,23), respectively; 21% (CI, 11% to 31%) for various mixed-status stage III-IV gastroenteropancreatic (GET) NETs (27); 22% (CI, 10% to 34%) for various progressive stage III-IV GET-NETs (27); 4% (CI, 0 - 8%) for various progressive stage IV carcinoid (32); and 36% (CI, 11% to 61%) and 39% (CI 12% to 66%) for endocrine pancreatic tumour in two studies, but the sample sizes were less than 30 altogether (19,23). For ^{90}Y-DOTALAN, the overall response rate was 18% (CI, 5% to 31%) for carcinoid patients (22). For ^{90}Y-DOTATATE, the overall response rate was 44% (CI, 27% to 61%) for various stage IV NETs in the Hubalewska-Dydejczyk et al study (29); 23% (CI, 12% to 34%) for various stage IV GEP-NET at six months, and 24% (CI, 7% to 41%) for foregut carcinoid and 18% (CI, 4% to 32%) for midgut carcinoid at six months from the subgroup analysis with the sample sizes smaller than 30 in the 2010 Cwikla et al study (33). For ^{177}Lu-DOTATATE, the overall response rate was 46% (CI, 40% to 52%) for various types of stage IV GEP-NET, 40% (CI, 33% to 47%) for carcinoid, 60% (CI, 49% to 71%) for non-functioning EPT, 75% (CI, 51% to 100%) for 12 gastrinoma patients in the 2008 Kwekkeboom et al study (30); and 24% (CI, 9% to 39%) for various stage IV GEP-NET patients who were progressive after they had benefit from the previous ^{177}Lu-DOTATATE treatment (34). Figure 2 shows the overall response rates by different PRRT.

Figure 2. Overall response rates with 95% confidence intervals by different PRRT.*



Abbreviations: PRRT = peptide receptor radionuclide therapy, lcl = lower confidence interval, ucl = upper confidence interval, H-D = Hubalewska-Dydejczyk.

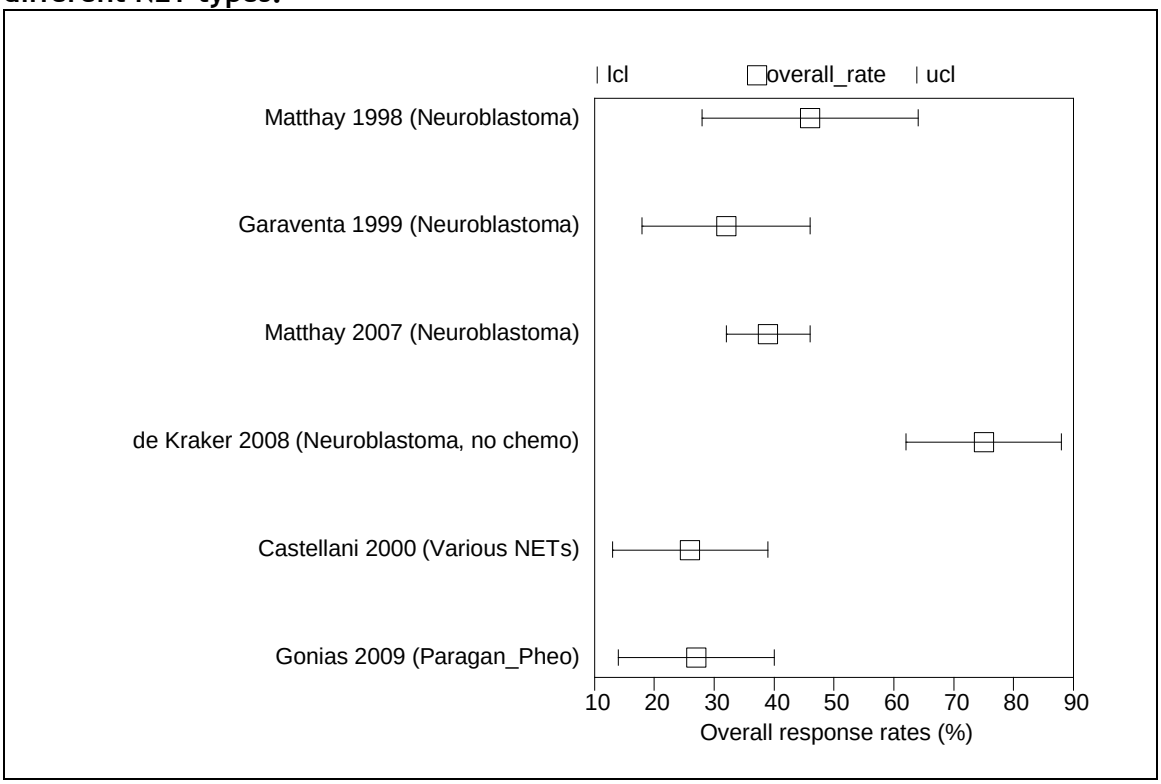
*The data were from the studies with a sample size of ≥30 patients who had not received prior PRRT.

2. ^{131}I-MIBG therapy

The data for tumour response on imaging were reported in six studies. Three studies used the 1993 version of the International Neuroblastoma Response Criteria (INRC) (41,45,46), one study used the 1988 INRC version (40), the 2000 Castellani et al study used the International Union Against Cancer criteria (42), and the 2009 Gonias et al study created its own criteria to assess tumour response (47) (see notes under Table 5b).

The overall response rate was 32% (CI, 18% to 46%) to 75% (CI, 62% to 88%) for stage III-IV neuroblastoma patients (40,41,45,46). Including the subgroup data of 21 neuroblastoma patients in the 2000 Castellani et al study (42) resulted in an expanded overall response rate of from 24% (CI, 6% to 42%) to 75% (CI, 62% to 88%). The overall response rate was 26% (CI, 13% to 39%) for patients with various stage III-IV NETs (42) and 27% (CI, 14% to 40%) for patients with stage IV paragangliomas or pheochromocytomas (47). Figure 3 shows the overall response rates by different NET types for studies with equal to or more than 30 patients.

Figure 3. Overall response rates for ^{131}I-MIBG therapy with 95% confidence intervals by different NET types.*



Abbreviations: NET = neuroendocrine tumour, lcl = lower confidence interval, ucl = upper confidence interval, chemo = chemotherapy, Paragan_Pheo = paraganglioma or pheochromocytoma.

*Data with the denominator ≥30 are shown.

Biochemical Responses

Very limited data for biochemical responses were available from the eligible studies (Table 6).

Symptomatic Responses and QOL

The self-reported assessment of QOL using five different tools was available in seven studies (19,23,22,25,26,32,33) for four therapeutic radiopharmaceuticals (^{90}Y-DOTATOC, ^{90}Y-DOTALAN, ^{90}Y-DOTATATE, and ^{177}Lu-DOTATATE) of PRRT (Table 7). The five tools were the National Cancer Institute (NCI) Common Toxicity Criteria; European Quality of Life-5 Dimensions (EQ-5D), a visual analogue scale; European Organization of Research and Therapy in Cancer Quality of Life Questionnaire C30 (EORTC QLQ-**C30**); and Quality of Life Questionnaire - gastrointestinal neuroendocrine tumours 21 (QLQ-G.I.NET21). The QOL improved for some patients in all studies, but no comparison among different studies or among different therapeutic radiopharmaceuticals can be made because of clinical heterogeneity.

Table 6. Outcomes of biochemical response.

Study	N for analysis (%)	Biochemical response
^{111}In-DTPAOC		
Valkema 2002 (21)	25 (50%)	Change in CgA levels was parallel to changes noted on CT in 18 pts and opposite in the other 7 pts; changes in CgA were nonsignificant during follow-up.
Nguyen 2004 (24)	19 (59%)*	5-HIAA was reduced by mean 65% in 3 pts, NSE was reduced by 37% in 1 pt.
^{90}Y-DOTATOC		
Iten 2007 (28)	31 (100%)	Calcitonin level decreased by median 45.2% (range 0.4-96.3%) in 9 pts.
^{177}Lu-DOTATATE		
Van Essen 2010 (34)	23 (70%) who had elevated CgA levels at the start of regular therapy (in Kwekkeboom 2008) and at the start of this study	Almost all patients had a clear decrease in CgA levels after regular therapy and a clear increase at the time of renewed disease progression before additional therapy. After additional therapy, CgA levels decreased mainly in the 6 pts with a minor response or partial remission.
^{131}I-MIBG		
Gonias 2009 (47)	31 (62%) for catecholamine/metanephrine, 34 (68%) for CgA	After first cycle of ^{131}I-metaiodobenzylguanidine treatment, 21 pts had CR, PR or MR on catecholamine/metanephrine level, and 25 pts had CR or PR on CgA level.†

Abbreviations: N = number of patients, CgA = chromogranin A, 5-HIAA = urinary 5-hydroxyindoleacetic acid, pts = patients, NSE = neuron-specific enolase.

*Fourteen patients were treated by ^{111}In-DTPAOC, and 5 patients were treated by ^{131}I-MIBG.
†CR = complete response defined as decreasing back to normal level, PR = partial response defined as ≥50% decrease in initially-elevated level, MR = mixed response (defined as any marker achieved PR or CR while others did not change).

Table 7. Quality of life.

Study	N for analysis (%)	Quality of life
^{90}Y-DOTATOC		
Waldherr 2001 (19)	41 (100%)	Assessed by NCI-CTC: 83% pts suffering from malignant carcinoid syndrome achieved a significant improvement. A reduction of pain score was observed in all 5 pts with morphine-dependent tumour-associated pain.
Waldherr 2002 (23)	21 (54%)	Assessed by a developed questionnaire using the NCI-CTC: the overall clinical benefit rate was 63%; 5 of 9 pts who had tumour-associated pain improved at least 1 grade.
Forrer 2006 (26)	57 (49%)	Assessed by NCI-CTC: Symptoms of malignant carcinoid syndrome decreased significantly: 83% pts with diarrhea, 46% with flushes, 63% pts with wheezing, and 75% pts with pellagra; pts with tumour-related pain achieved a significant reduction.
Bushnell 2010 (32)	78 (87%)	Assessed by EQ-5D: 24% for usual activities, 28% for anxiety/depression, 29% for pain/discomfort, 21% for mobility, and 6% for self-care showed a durable improvement. 61% had a durable response on general health state scale.
^{90}Y-DOTALAN		
Virgolini 2002 (22)	39 (100%)	Cancer-related pain was assessed by a visual analogue scale: 5 carcinoid pts and 1 GEP-NET pt improved.
^{90}Y-DOTATATE		
Cwikla 2010 (33)	60 (100%)	Assessed by EORTC QLQ-C30 and QLQ-GI.NET21: Among pts with symptoms, 15 of 24 had pain reduction during therapy or 4-8 weeks after PRRT and 3 pts had recurrence later, 10 of 19 had diarrhea reduction, 9 of 11/12 had flushing reduction*, 14 of 20 regained weight. 16% pts had significant improvement for WHO performance status.
^{177}Lu-DOTATATE		
Teunissen 2004 (25)	50 (100%)	Assessed by EORTC QLQ-C30: global health status/QOL, role, emotional, and social function scores were significantly improved; symptom scores for fatigue, insomnia, and pain were significantly decreased, especially in those patients with proven tumour regression. Patients with progressive disease also indicated an improvement in global health/QOL score.

Abbreviations: N = number of patients, NCI-CTC = National Cancer Institute - Common Toxicity Criteria, pts = patients, EQ-5D = European Quality of Life-5 Dimensions, EORTC QLQ-C30 = European Organization of Research and Therapy in Cancer Quality of Life Questionnaire C30, QLQ-GI.NET21 = Quality of Life Questionnaire - gastrointestinal neuroendocrine tumour 21, WHO = World Health Organization, QOL = quality of life, NR = not reported.

*Flushing was reported in 11 patients before therapy on page 791, but it was reported in 12 patients before therapy on page 793.

Toxicity

1. Peptide Receptor Radionuclide Therapy

Data on toxicity from PRRT are summarized in Table 8a. The WHO criteria were used for toxicity grading in seven articles (20-22,29,30,32,33) and the National Cancer Institute (NCI) grading criteria in four articles (19,23,26,28), and three articles did not specify toxicity criteria (24,27,34). Nausea and vomiting were common during therapy. The severe toxicities included: for ^{111}In-DTPAOC, 8% of patients developed myelodysplastic syndrome (MDS) and/or leukemia in one study (21); for ^{90}Y-DOTATOC, 0.9-3.4% of patient developed grade 4 renal toxicity in three studies (26-28), and 2% of patient developed MDS in one study (27); for ^{90}Y-DOTALAN, no severe toxicity was found in one study (22); for ^{90}Y-DOTATATE, 30% of patients developed grade 2 renal toxicity at two years in one study (33); for ^{177}Lu-DOTATATE, 0.6% of patients developed hepatic insufficiency, 0.8% developed MDS, and 0.4% developed renal insufficiency in one study (30). For studies investigating the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, and ^{177}Lu-DOTATATE, lysine and arginine amino acid solution was infused to protect kidney function for each patient.

2. ^{131}I-MIBG therapy

Toxicity data after ^{131}I-MIBG therapy are summarized in Table 8b. The WHO criteria were used for toxicity grading in the Garaventa et al study (41), while the Common Terminology Criteria for Adverse Events version 2.0 was used in the 2007 Matthay et al study (45) and version 3.0 in the 2009 Gonias et al study (47). Other studies did not specify the criteria used for assessing toxicity. Hematologic toxicities were the main severe side effects. Forty-three percent of patients required bone marrow replacement (BMR) (21% of these patients had prior myeloablative therapy), and one patient with seven years of alkylating agents and etoposide therapy developed secondary leukemia in the 1998 Matthay et al study (40). Five percent of patients in the Garaventa et al study (41) and 2% in the 2007 Matthay et al study (45) who had had heavy pretreatments developed leukemia or MDS, while 39% needed autologous BMR, and 9% died (three due to multifocal infections) in the 2008 de Kraker et al study (46). It is noteworthy that after accumulative doses of at least 63.3 GBq ^{131}I-MIBG therapy, 4% of patients who did not have prior radiation or chemotherapy developed MDS and acute myeloid leukemia at two and five years in the Gonias et al study. In addition, 4% developed acute respiratory distress syndrome, 4% developed bronchiolitis obliterans organizing pneumonia, and 2% had pulmonary embolism in this same study (47).

Garaventa et al reported that five (4%) three- to five-year-old children with stage III-IV neuroblastoma developed secondary malignancies after ^{131}I-MIBG therapy being used either as part of the first-line therapy or as salvage therapy for resistant or recurrent disease: one acute nonlymphoblastic leukemia at one and a half years, one chronic myelomonocytic leukemia at four years, one malignant schwannoma at seven years, one rhabdomyosarcoma at 14 years, and one angiomatoid malignant fibrous histiocytoma at 10 years after ^{131}I-MIBG (43).

Table 8a. Toxicity from peptide receptor radionuclide therapy.

Study	N for analysis (%)	Kidney-protecting agent	Gastrointestinal toxicity	Haematologic toxicity	Genitourinary toxicity	Other toxicity
^{111}In-DTPAOC						
Valkema 2002 (21)*	40 (80%)	NR	NR	MDS and/or leukaemia with grade 4 platelet: 3 pts; platelet transfusion: 2 pts (1 pt had prior external-beam radiation therapy); grade 3 lymphocyte: 18 pts and grade 4: 12 pts; grade 3 anaemia: 7 pts	Grade 1 toxicity serum creatinine: 1 pt	In men: after 20-30 GBq, serum inhibin B significantly decreased; after 50-70 GBq, FSH and LH levels significantly higher
Nguyen 2004 (24)†	19 (95%) in intervention group	No	No significant toxicity	No significant toxicity by ^{111}In-DTPAOC; pancytopenia: 1 of 5 pts by ^{131}I-MIBG	No significant toxicity	No significant toxicity
^{90}Y-DOTATOC						
Waldherr 2001 (19)‡	41 (100%)	8% amino acid at 0.5 h before PRRT	Nausea, vomiting and flush during injection: 11 pts; no other significant toxicity	grade 1-3 lymphocytopenia: 14 pts; grade 3 anaemia and thromobocytopenia: 2 pts	No	NR
Waldherr 2002 (23)‡	39 (100%)	8% amino acid 500 mL at 0.5 h before PRRT and 2000 mL after PRRT	During injection, nausea: 48% pts and vomiting: 29%; no other significant toxicity	Grade 3-4 lymphocytopenia: 23%; grade 3 anaemia: 3%. All toxicities were reversible.	Grade 2 renal toxicity: 1 pt at 5 mo after PRRT	NR
Paganelli 2002 (20)*	87 (100%)	L-lysine and L-arginine amino acids	Nausea and vomiting (grade 1-2): 50% pts	Grade 3 toxicity WBC and/or platelets: 3 pts with 5.18 GBq/cycle	Grade 1 renal toxicity: 2 pts	NR
Forrer 2006 (26)‡	116 (100%)	8% amino acid 0.5 h before PRRT up to 3.5 h	Nausea and vomiting: 23% pts within 24 h after PRRT	Grade 3 lymphopenia: 9 pts; grade 3 pancytopenia: 3 pts	Grade 4 renal toxicity: 1 pt	NR
Valkema 2006 (27)†	58 (100%)	2000 mL of amino acid solution 0.5 h before PRRT	Dose-limiting grade 3 liver toxicity: 1 pt	Dose-limiting grade 4 thromobocytopenia: 1 pt; MDS: 1 pt at 2 y	9 (16%) pts had >15% decline/y in CCr and 2 pts had end-stage renal disease	NR
Iten 2007 (28)‡	31 (100%)	2000 mL of amino acid solution 0.5 h before PRRT until 3 h after PRRT	Grade 1 nausea: 5 pts	Grade 2 transient leucopenia: 3 pts; grade 3 transient thrombopenia: 1 pt.	Renal toxicity: 2 pts transient grade 1, 3 pts permanent grade 1, and 1 pt grade 4 at 26 months	NR
Bushnell 2010 (32)*	90 (100%)	2000 mL of amino acid solution with about 28 g of both lysine and arginine 0.5 h before PRRT to over 4 h	A dosage adjustment or interruption of PRRT: 12 pts; discontinued PRRT: 9 pts			
			Grade 3-4 nausea, vomiting, and abdominal pain (associated with amino acid): 27 pts (36%); grade 3-4 diarrhea: 5 pts; grade 3 ascites: 3 pts; grade 3 constipation: 1 pt	Grade 3-4 lymphopenia: 14 pts	Grade 3 oliguria: 1 pt, grade 3 dysuria: 1 pt, and grade 4 renal failure: 1 pt; they lasted 6, 42, and 6 days, respectively	Grade 3-4 asthenia: 6 pts; grade 3 fatigue: 6 pts; grade 3 anorexia: 5 pts; grade 3-4 carcinoid syndrome: 6 pts, grade 3 flushing: 7 pts
^{90}Y-DOTALAN						
Virgolini 2002 (22)*	39 (100%)	No	No change in liver function parameters caused by PRRT	No severe acute or chronic haematological toxicity	No	NR

^{90}Y-DOTATATE						
Hubalewska-Dydejczyk 2008 (29)*	32 (100%)	L-lysine and L-arginine amino acid before and after PRRT	NR	Grade 3 on leucocytosis: 3 pts; grade 3 platelet: 1 pts; grade 3 anaemia: 3 pts	No	NR
Cwikla 2010 (33)*	60 (100%) after PRRT	1500 mL amino acid (13.5 g lysine and 17 g arginine in each infusion) 1.5-2 h before PRRT	In the first cycle, mild nausea: 9 pts; vomiting: 5 pts (some due to amino acid); flushing: 3 pts; abdominal pain: 4 pts	Grade 3-4 leucopoenia:5 pts; grade 3-4 anaemia 6 pts; grade 3 platelet depletion: 1 pt	No significant renal toxicity	Headaches in the first cycle: 2 pts
	57 (95%) at 6 weeks after PRRT		No	Grade 3-4 thrombocytopenia: 2 pts (4%), grade 3 leucopenia and anaemia: 1 pt	No significant renal toxicity	NR
	56 (93%) at 6 mo		No	Grade 3 thrombocytopenia: 1 pt	No significant renal toxicity	NR
	40 (67%) at 12 mo		No	Grade 3 anaemia: 2 pts; grade 3 thrombocytopenia: 1 pt	Renal toxicity grade 2: 3 pts; grade 3: 2 pts	NR
	23 (38%) at 24 mo		No	No	Grade 2 renal toxicity: 7 pts	NR
^{177}Lu-DOTATATE						
Kwekkeboom 2008 (30)*	504 (100%)	2.5% Lysine and 2.5% arginine starting 0.5 h before PRRT up to 4h	Nausea, vomiting, and abdominal discomfort or pain; hepatic insufficiency: 3 pts with liver metastases	Grade 3-4 haematological toxicity: 9.5% pts; MDS: 4 pts (1 pt had previous chemotherapy with alkylating agents)	Renal insufficiency: 2 pts (1 pt had prior kidney function deterioration; 1 had increasing tricuspid valve insufficiency)	Hormonal crises: 6 pts hospitalized; grade 1 hair loss: 62% pts
Teunissen 2009 (31)§	35 (90%) men; 66 (84%) for thyroid hormone analysis	2.5% lysine and 2.5% arginine starting 0.5 h before PRRT up to 4h	Endocrine function toxicities: In 35 men, mean serum inhibin B decreased at 3 mo (205 to 25 ng/L, $p<0.05$) and FSH increased (5.9 to 22.7 IU/L, $p<0.05$). These levels returned to near baseline levels later, but the inhibin B was significantly decreased at 24 mo. TT and SHBG decreased (15.0 to 10.6 nmol/L, $p<0.05$ and 61.8 to 33.2 nmol/L, $p<0.05$), respectively at 24 mo. An increase of LH level (5.2 to 7.7 IU/L, $p<0.05$) at 3 mo and returned to baseline levels later. In 21 postmenopausal women, a decrease in levels of FSH (74.4 to 62.4 IU/L, $p<0.05$) and LH (26.8 to 21.1 IU/L, $p<0.05$). Of 66 patients, two developed persistent primary hypothyroidism. FT_4 level decreased (17.7 to 15.6 pmol/L, $p<0.05$). rT_3 decreased (0.38 to 0.30 nmol/L, $p<0.05$). ACTH stimulation test showed an adequate response of serum cortisol (>550 nmol/L, n=18). Five patients developed elevated HbA_{1c} (>6.5%).			
Van Essen 2010 (34)†	33 (100%)	2.5% lysine and 2.5% L-arginine starting 0.5 h before PRRT to 4 h	NR	Grade 3-4 thrombocytopenia: 5 pts	No kidney failure	NR

Abbreviations: N = number of patients, pts = patients, MDS = myelodysplastic syndrome, GBq = gigabecquerel, FSH = follicle-stimulating hormone, LH = luteinizing hormone, mL = millilitres, h = hours, PRRT = peptide receptor radionuclide therapy, mo = months, WBC = white blood cell, y = years, CCr = creatinine clearance rate, g = gram, ng = nanogram, L = litre, IU = international unit, p = p-value, nmol = nanomole, pmol = picomole, TT = total testosterone, SHBG= sex hormone binding globulin, FT_4 = free thyroxine, T_3 = triiodothyronine, rT_3 = reverse triiodothyronine, ACTH = adrenocorticotropic hormone, HbA_{1c} = glycosylated haemoglobin, NR = not reported.

*The World Health Organization criteria were used for toxicity grading.
†No criteria for toxicity grading were reported.
‡The National Cancer Institute grading criteria were used for toxicity grading.
§Endocrine functions were analyzed in 79 local resident pts from the Kwekkeboom 2008 study, so the kidney-protecting agent should be the same as that in Kwekkeboom 2008.

Table 8b. Toxicity from ^{131}I-MIBG Therapy.

Study	N for analysis (%)	Toxicity-protecting agent	Hematologic toxicity	Other toxicity
Matthay 1998 (40)*	30 (100%)	$KClO_4$ and KI 1 hour before ^{131}I-MIBG to 21 d or for 42 d for pt with 0.67 GBq/kg MIBG; a Foley catheter	After first cycle among 29 pts: grade 4 thrombocytopenia: 62% pts and 46% had ANC < 500/μL; grade 4 thrombocytopenia and/or neutropenia: 80% pts among pts with 0.44 GBq/kg ^{131}I-MIBG; 43% pts had BMR in pts with ≥ 0.56 GBq/kg ^{131}I-MIBG. After other cycles among 10 pts: BMR: 4 pts, secondary leukemia: 1 pt with 7 previous years of alkylating agents and etoposide	Mild nausea and vomiting during the first 2 d: most pts; grade 2 hypertension during infusion: 2 pts; mouth dryness: 3 pts; asymptomatic hypothyroidism: 2 pts
Garaventa 1999 (41)†	43 (100%)	Iodine given for 5 d before and 8 d after MIBG	In stage III pts, grade 3: 3 pts and grade 4 thrombocytopenia: 2 pts. In stage IV pts among 58 assessed courses, grade 4 thrombocytopenia: 19 times; myeloid leukemia: 2 pts with heavy chemotherapy before ^{131}I-MIBG	Interstitial pneumopathy that resulted in death: 1 pt; hypothyroidism requiring replacement treatment: 15 pts
Castellani 2000 (42)*	37 (82%)	Oral iodine	Grade 2-3: 15 pts	Hypothyroidism: 5 pts; hypotension: 1 pt
Garaventa 2003 (43)‡	119 (100%)	Iodine 5 d before until 8 d after ^{131}I-MIBG	Acute nonlymphoblastic leukaemia that resulted in death: 1 pt at 1.5 y after ^{131}I-MIBG; chronic myelomonocytic leukaemia: 1 pt at 4 years after ^{131}I-MIBG and died of chronic graft-versus-host disease	Malignant schwannoma that resulted in death: 1 pt at 7 y after ^{131}I-MIBG; rhabdomyosarcoma that resulted in death: 1 pt at 14 y after ^{131}I-MIBG; angiomatoid malignant fibrous histiocytoma: 1 pt
Matthay 2007 (45)§	164 (100%)	$KClO_4$ and KI; a Foley catheter	HCT: 49 pts; PT: 76 pts among pts with 0.67 GBq/kg MIBG and 12 pts among pts with 0.44 GBq/kg ^{131}I-MIBG; MDS/AML: 4 pts with heavy pretreatments	For nonhematologic toxicities, grade 3: 36 pts and grade 4: 15 pts, including 34 infectious episodes and 18 proven infections; retroperitoneal mesothelioma: 1 pt; asymptomatic grade 1 hypothyroidism: some pts
de Kraker 2008 (46)*‖	44 (100%)	KI for 14 d	Autologous BMR: 17 pts; death: 4 pts	Elevated TSH: 10 of 22 assessed pts and 5 pts needed thyroxine treatment
Gonias 2009 (47)¶	49 (98%)	$KClO_4$ and KI; a Foley catheter	Grade 3-4 neutropenia: 87% pts; grade 3-4 thrombocytopenia: 83% pts; grade 3-4 anaemia: 8% pts; MDS and acute myeloid leukaemia: 2 pts with at least 63.3 GBq and none of them had prior radiation or chemotherapy	Acute respiratory distress syndrome: 2 pts; bronchiolitis obliterans organizing pneumonia: 2 pts; pulmonary embolism: 1 pt; fever with neutropenia: 7 pt; acute hypertension: 10 pts; hypogonadism: 4 pts; infection: 1/2 pts#

Abbreviations: N = number of patients, $KClO_4$ = potassium perchlorate, KI = potassium iodide, d = day, pt = patient, kg = kilogram, ANC = absolute neutrophil count, μL = microlitre, BMR = bone marrow replacement, y = year, HCT = hematopoietic cell transplant, PT = platelet transplantation, MDS = myelodysplasia syndrome, AML = acute myeloblastic leukemia, TSH = plasma thyrotrophin.

*****No criteria for toxicity grading were specified.

†The World Health Organization criteria were used for toxicity grading.

‡ Outcome of this study only focused on secondary malignancy; all these 5 pts had prior chemotherapy.

§The Common Terminology Criteria for Adverse Events version 2.0 were used for toxicity grading.

‖Hematologic toxicity was assessed before surgery etc. treatments.

¶The Common Terminology Criteria for Adverse Events version 3.0 were used for toxicity grading.

#It showed 2 patients in the original abstract, but 1 patient in Table 2 on page 4164.

ONGOING TRIALS

The NCI clinical trials database (http://www.cancer.gov/clinicaltrials) was searched on December 20, 2010, and the European Clinical Trial Register (https://www.clinicaltrialsregister.eu/) was searched on June 1, 2011 for the potential trials meeting the eligibility criteria. Seven relevant trials for PRRT and seven relevant trials for ^{131}I-MIBG therapy were found, and details appear in Tables 9a and 9b. One external reviewer provided a link of an ongoing RCT that was registered at the Netherland clinical trial website (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=913). It was added in Table 9a.

Table 9a. Four ongoing trials for peptide receptor radionuclide therapy.

1. Safety and Efficacy Study of In-111 Pentetreotide to Treat Neuroendocrine Tumours Phase: Phase III, Phase II Type: Treatment Status: Active Age: 18 and over Sponsor: Other Protocol IDs: 06-2247, NCT00442533 Estimated sample size: 100 Expected completion: August 2011 Description: The purpose of this study is to determine if High-dose 111In-Pentetreotide (3 cycles of 18.5 GBq every 10-12 weeks), known as NeuroendoMedix®, is an effective treatment for neuroendocrine tumour.
2. DOTA-TOC in Metastasized Neuroendocrine Cancer Phase: Phase II Type: Treatment Status: Active Age: Not specified Sponsor: Other Protocol IDs: MAW002, NCT00978211 Estimated sample size: 1500 Expected completion: May 2011 Description: The investigators aim to explore the efficacy of [90Y-DOTA]-TOC and [177LuDOTA]-TOC therapy in advanced neuroendocrine cancer. Therefore, the investigators investigate response, survival and long-term safety profile of systemic [90Y-DOTA]-TOC and [177LuDOTA]-TOC treatment in metastasized neuroendocrine cancer patients. Adverse events are assessed according to the criteria of the National Cancer Institute. Survival analyses are performed using multiple regression models.
3. 177Lutetium-DOTA-Octreotate Therapy in Somatostatin Receptor-Expressing Neuroendocrine Neoplasms Phase: No phase specified Type: Treatment Status: Active Age: 18 and over Sponsor: Other Protocol IDs: 78,256, NCT01237457 Estimated sample size: Unclear Expected completion: October 2013 Description: To confirm the safety and effectiveness of 177Lu-DOTATATE therapy for somatostatin receptor-expressing cancers including, but not limited to, those arising from the neural crest and involving such organs as the lungs, breast, gastrointestinal tract, skin and endocrine (examples: pheochromocytoma, medullary carcinoma of the thyroid, non-radioiodine-avid differentiated thyroid cancer, melanoma, renal cell, Merkel cell, paraganglioma, small cell lung, carcinoid and pancreatic islet cell malignancies).

4. Neo-adjuvant Peptide Receptor Mediated Radiotherapy With 177Lutetium in Front of Curative Intended Liver Transplantation in Patients With Hepatic Metastasis of Neuroendocrine Tumours (NEO-LEBE)
Phase: No phase specified
Type: Treatment
Status: Active
Age: 18 to 60
Sponsor: Other
Protocol IDs: NEO-LEBE, NCT01201096
Estimated sample size: 50
Expected completion: September 2018
Description:
The purpose of this study is to show the tumour free long-term survival of patients with isolated non-resectable liver metastases of neuroendocrine tumours after neo-adjuvant radio receptor treatment and following liver transplantation.

5. Best Therapy for Patients With Neuroendocrine Tumours
Phase: No phase specified
Type: Treatment
Status: Active
Age: 18 to 90
Sponsor: Other
Protocol IDs: ZBB-NET-1, NCT00815620
Estimated sample size: 210
Expected completion: November 2012
Description:
A prospective observational study containing three arms comprising different therapeutic measures to treat patients with neuroendocrine tumors in advanced stages. The therapy arms include local ablative therapy such as TACE or SIRT, surgery, and RFA with peptide receptor radiotherapy.

6. An open, non-randomized phase-2 study of efficacy and safety of treatment with 177Lutetium-DOTA0-Tyr3-octreotate in patients with neuroendocrine tumors
Phase: phase II
Type: Treatment
Status: Active
Age: 18 and over
Sponsor: Department of Endocrine Oncology
EudraCT number: 2009-012260-14
Estimated sample size: 100
Start Date: 2010-08-27
Main objective:
Clarify the effect of the treatment with 177-Lu-DOTA-octreotate, regarding a) tumour size, b) biochemical response, c) prognostic factors such as proliferation markers and LD/ALP and type of tumour, d) quality of life, e) survival, and f) progression-free survival.

7. Receptor radionuclide therapy with [177Lu- DOTA]0,Tyr3-octreotate (177Lu-DOTATATE): a phase II trial.
Phase: phase II
Type: Treatment
Status: Active
Age: 18 and over
Sponsor: ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI
EudraCT number: 2007-005517-20
Estimated sample size: 200
Start Date: 2008-01-10
Main objective:
To evaluate the objective response of 177Lu-DOTATATE treatment in patients affected by sst2 positive tumours.

8. A multicenter study comparing treatment of patients with neuroendocrine Gastro-Entero-Pancreatic (GEP) tumours with 177Lu-octreotate versus combined 177Lu-octreotate and capecitabine treatment.
Phase: Randomized trial
Type: Treatment
Status: Active
Age: Unclear
Sponsor: Erasmus Medical Center, Department of Nuclear Medicine
NTR Number: NTR913
ISRCTN: ISRCTN30356763
Estimated Enrolment: 200
Estimated Primary Completion Date: 2010*
Description:
This trial is comparing 177Lu-DOTATATE (arm 1) with 177Lu-DOTATATE plus capecitabine (arm 2) in patients with GEP tumours. Efficacy and safety assessments Objective response as determined by the Southwest Oncology Group criteria is the main efficacy endpoint.

*No published paper had been found by Nov. 4, 2010.

Table 9b. Seven ongoing trials for ^{131}I-metaiodobenzylguanidine therapy.

1. Phase II Pilot Study of Targeted Radiotherapy Using Iodine I 131 Metaiodobenzylguanidine in Patients With Recurrent, Progressive, or Refractory Neuroblastoma or Malignant Chromaffin Cell Tumours
Phase: Phase II
Type: Treatment
Status: Active
Age: Over 1
Sponsor: Other
Protocol IDs: MSKCC-04148, NCT00107289
Estimated Enrolment: 38
Estimated Primary Completion Date: 2010*
Description:
This trial is studying how well giving iodine I 131 metaiodobenzylguanidine works in treating patients with recurrent, progressive, or refractory neuroblastoma or malignant pheochromocytoma or paraganglioma.

2. Iodine I 131 Metaiodobenzylguanidine, Combination Chemotherapy, and Radiation Therapy in Treating Patients Who Are Undergoing an Autologous Peripheral Stem Cell or Bone Marrow Transplant for Relapsed or Refractory Neuroblastoma
Phase: Phase II
Type: Treatment
Status: Active
Age: 1 to 29
Sponsor: NCI, Other
Protocol IDs: CDR0000450148, NANT-2001-02, NCT00253435
Estimated Enrolment: 50
Estimated Primary Completion Date: 2010*
Description:
This trial is studying how well giving iodine I 131 metaiodobenzylguanidine together with combination chemotherapy and radiation therapy works in treating patients who are undergoing an autologous peripheral stem cell or bone marrow transplant for relapsed or refractory neuroblastoma.

3. Efficacy and Safety of Ultratrace™ Iobenguane I 131 in Neuroblastoma
Phase: Phase II
Type: Treatment

Status: Approved-not yet active
Age: 1 and over
Sponsor: Pharmaceutical / Industry
Protocol IDs: MIP-IB-N201, NCT00992173
Estimated Enrolment: 100
Estimated Primary Completion Date: June 2013
Description:
In this study the investigators are investigating the use of a new form of Iobenguane I 131 called Ultratrace iobenguane I 131. This form is expected to deliver higher amounts of radioactive I 131 to the neuroblastoma cells. The primary purpose of the study is to determine if Ultratrace iobenguane I 131 can be used to successfully treat high-risk neuroblastoma. The study will also assess the safety of Ultratrace iobenguane I 131 when given to patients with high-risk neuroblastoma.

4. N2007-03: Vorinostat and 131-I MIBG in Treating Patients With Resistant or Relapsed Neuroblastoma
Phase: Phase I
Type: Biomarker/Laboratory analysis, Treatment
Status: Active
Age: 2 to 30
Sponsor: NCI, Other
Protocol IDs: CDR0000659059, P01CA081403, N2007-03, NANT-N2007-03, NCT01019850
Estimated Enrolment: 42
Estimated Primary Completion Date: December 2012
Description:
This phase I trial is studying the side effects and best dose of giving vorinostat together with iobenguane I 131 in treating patients with resistant or relapsed neuroblastoma.

5. 131-I-MIBG Therapy for Refractory Neuroblastoma and Metastatic Pheochromocytoma (CHP-830)
Phase: No phase specified
Type: Treatment
Status: Active
Age: 1 and over
Sponsor: Other
Protocol IDs: 2005-02-4159, NCT01163383
Estimated Enrolment: 250
Estimated Primary Completion Date: July 2015
Description:
The purpose of this research is to gain further evidence of the effectiveness of this treatment and to further assess the side effects of ^{131}I-MIBG therapy.

6. A Study Evaluating Ultratrace Iobenguane I 131(MIBG) in Patients With Malignant Pheochromocytoma/Paraganglioma
Phase: Phase II
Type: Treatment
Status: Active
Age: 12 and over
Sponsor: Pharmaceutical / Industry
Protocol IDs: MIP-IB12B, NCT00874614
Estimated Enrolment: 75
Estimated Primary Completion Date: June 2015
Description:

The purpose of this trial is to test the use of Ultratrace iobenguane I 131 as a treatment for pheochromocytoma and paraganglioma type cancer. This Phase II study will help determine primarily if using the drug reduces the amount of blood pressure medication being taken as a result of the cancer and secondarily to determine such things as the effectiveness of the study drug in treating the cancer, additional safety measures and to assess if the drug helps the quality of life and use of pain medication. All subjects will receive an imaging dose with scans followed by two therapy doses that are given 3 months apart.
7. Phase III/IV Randomized Study of Risk-Adapted Therapy Comprising Observation Only, Combination Chemotherapy, Radiotherapy, and/or Autologous Stem Cell Transplantation in Younger Patients With Neuroblastoma† Phase: Phase IV, Phase III Type: Treatment Status: Active Age: 21 and under Sponsor: Other Protocol IDs: GPOH-NB2004, EU-20661, NCT00410631 Estimated Enrolment: 642 Estimated Primary Completion Date: December 2010 Description: This trial is studying observation, combination chemotherapy, radiation therapy, and/or autologous stem cell transplant to compare how well they work in treating young patients with neuroblastoma. Patients are stratified according to disease risk (low-risk vs medium-risk vs high-risk).

*No published paper had been found by Nov. 4, 2010.
†This trial does not include a randomization concerning ^{131}I-metaiodobenzylguanidine therapy.

DISCUSSION

1. Peptide Receptor Radionuclide Therapy

Somatostatin has hormone inhibitory effects, and some of the somatostatin receptors (SSTRs) also mediate the inhibition of cell proliferation, but receptor activation is not a primary cytotoxic target. Nevertheless, SSTR expression provides a means of targeting cytotoxic radiation to tumours that express them at high levels, by the administration of a radiolabeled ligand.

Three articles reported that patients with CR, PR, or SD after PRRT had longer OS time than did patients with PD (30,33,34). These findings seem to support that PRRT may be effective in NET patients who are positive on octreoscan and who respond to PRRT.

To date, no RCTs comparing two radiolabeled somatostatin analogues have been published. Thus, no strong conclusion can be made that one therapeutic radiopharmaceutical of PRRT is more effective than others for malignant NET patients. However, ^{177}Lu-DOTATATE seems more effective than ^{111}In-DTPAOC and ^{90}Y-DOTATOC from the comparisons with historical controls. The results from these comparisons, though, should be interpreted with caution (30).

It seems that ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE have good tumour response rates for various NETs, especially for carcinoid patients, compared with other therapeutic radiopharmaceuticals from Table 5a and Figure 2. However, the investigators of most included studies already had predetermined that PRRT would be effective in malignant NET patients, and no blinded assessment of outcomes were specified (Table 4). Thus, these prospective studies might overestimate PRRT effects. Additionally, ^{177}Lu-DOTATATE seems to have longer median survival time than does ^{90}Y-DOTATATE from Table 5a (46 vs. 22 months) (30,33), but again, without an RCT, no strong conclusion can be made.

Phase I or II trials are unlikely to provide convincing evidence for treatment effects, but observational studies are often the only way to detect treatment toxicity (54). Except for the Hubalewska-Dydejczyk et al study (29), 15 articles specified that patients had various treatments before PRRT. Cwikla et al reported that anemia after PRRT was observed in 35% of patients treated with previous chemotherapy and only in 10% who were not (33). Therefore, some hematologic toxicity evident in PRRT studies may be associated with previous chemotherapy and/or external-beam radiation therapy or other systemic therapy. Although kidney-protecting agents (lysine and arginine amino acid solutions) were used in most studies, at least grade 2 renal toxicity was still observed in six studies (21,26,27,28,30,33).

There are many unknown aspects of PRRT for malignant NET patients whose tumours were positive on octreoscan. For instance, the PRRT studies to date have been largely focused on terminal patients with a "salvage" approach. There have been no studies to determine the impact of this novel targeted therapy either in early-stage disease or for patients with a recent diagnosis of metastasis who might benefit from this therapy while they still have relatively limited tumour bulk. In addition, few data were available for biochemical response after PRRT. No high-quality studies compared PRRT alone or plus other treatments with chemotherapy. Kwekkeboom et al reported that the radiation emitted from ^{177}Lutetium had a lower tissue penetration range than that from ^{90}Yttrium and postulated that ^{177}Lu-DOTATATE might be especially important for small NETs, but the association between tumour size and effectiveness was not discussed further (55).

Seven ongoing trials were identified through a search of the NCI clinical trials database and European Clinical Trial Register, but none was an RCT. Walter et al in Switzerland (the second study in Table 9a) explored the efficacy of ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC in advanced NET patients and their main results were just published in June 2011 (56). During a median follow-up of 23 month on 1109 patients, longer survival was found in patients with morphologic, biochemical, or clinical response. The overall tumour response rate was 34.1%, which is consistent with the reports from other included articles on ^{90}Y-DOTATOC. However, it found that 9.2% of patients experienced grade 4-5 permanent renal toxicity, especially for older patients with low glomerular filtration rate or high renal tracer uptake at the baseline. An additional ongoing RCT provided by an external reviewer, comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATATE plus capecitabine in patients with GEP-NET, might provide useful information when its data is published (the eighth study in Table 9a).

2. ^{131}I-MIBG therapy

For malignant NET patients with negative uptake on octreoscan or renal insufficiency and positive uptake on ^{123}I-MIBG scintigraphy, ^{131}I-MIBG therapy may be a treatment option, and especially for pediatric patients with neuroblastoma. For stage IV neuroblastoma patients with a median age of 2.6 years and without prior chemotherapy (some patients had initial surgery), the overall response rate (75%) was high compared with other overall response rates in Figure 3 (46). It seems that ^{131}I-MIBG therapy may be a good choice as the first-line therapy for pediatric neuroblastoma patients. However, the hematologic toxicity, severe infections, and secondary malignancies after ^{131}I-MIBG therapy need to be considered, especially in high doses, although some toxicity may be related to prior treatments. Nonetheless, the fact that most of these patients are in the pediatric age group may be another reason for the high toxicities observed. Another important point is that, through the medical literature search (MEDLINE and EMBASE searched on February 8, 2011), no RCT existed to support the theory that ^{131}I-MIBG therapy was effective for any cancers.

Seven ongoing trials were identified from the NCI clinical trials database. Six of them are non-RCTs. Mertens et al in Germany (the seventh study in Table 9b) are conducting a phase III/IV RCT to study observation, combination chemotherapy, radiation therapy, and/or

autologous stem cell transplant to compare their effectiveness in treating young patients with neuroblastoma. This trial plans to enrol 642 patients, and the estimated primary completion date was December 2010. However, no publication of this study was found by the search date of this systematic review (November 4, 2010). Although this trial is an RCT, ^{131}I-MIBG therapy was not addressed under a randomized setting (57). Thus, despite these ongoing trials will been done in the future, RCTs about the effect of ^{131}I-MIBG in NET patients are still lacking.

CONCLUSIONS

To date, PRRT appears to be an acceptable option in adult patients with neuroendocrine cancer who are inoperable, who have residual disease following surgery or other ablative therapy, or who have metastases. Although no strong evidence (i.e., RCT) exists to determine which of the therapeutic radiopharmaceuticals (Table 1) is more effective, limited evidence based on a historical comparison of studies from a single centre showed that ^{177}Lu-DOTATATE might be associated with greater OS, PFS, and overall response rate compared with ^{90}Y-DOTATOC and ^{111}In-DTPAOC. The evidence showed that PRRT is relatively safe with renal protection of lysine and arginine amino acid solution in adult patients with advanced NETs, especially for ^{90}Y-DOTALAN and ^{177}Lu-DOTATATE. However, patients' renal functions must be monitored. ^{131}I-MIBG may be effective for malignant neuroblastoma or paraganglioma/pheochromocytoma, but insufficient evidence exists to suggest its efficacy for adult neuroendocrine carcinoma patients. The hematologic toxicity, severe infections, and secondary malignancies after ^{131}I-MIBG therapy should be considered. Well-designed and good-quality RCTs are required to investigate the further effectiveness of PRRT in NET patients (including the comparison among PRRT, and comparing PRRT with other treatment options such as chemotherapy or biotherapy plus PRRT or not, etc.). Additionally, well-designed and good-quality RCTs to investigate the further effect of ^{131}I-MIBG (including comparing ^{131}I-MIBG with other treatment options plus ^{131}I-MIBG or not, etc.) in malignant NET patients with negative uptake on octreoscan or renal insufficiency and positive uptake on ^{123}I-MIBG scintigraphy are encouraged.

JOURNAL REFERENCE

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CONFLICT OF INTEREST

The details of the authors' conflict of interest are shown at the end of Section 3.

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Appendix 1. Members of the Radionuclide Therapy for Neuroendocrine Cancer Expert panel and Working Group.

Expert Panel

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Working Group

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Ms. Xiaomei Yao, Research Coordinator, Program in Evidence-based Care, Cancer Care Ontario, Hamilton, Ontario

Appendix 2. MEDLINE searching for neuroendocrine cancer.

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1950 to Present

Search Strategy:

#	Searches	Results
1	((radionuclide$ adj2 therap$) or (radioisotope$ adj2 therap$) or salvage therap$ or (radiopharmaceutical$ adj2 therap$) or PRRT$).mp.	10571
2	((radionuclide$ adj2 treat$) or (radioisotope$ adj2 treat$) or salvage treat$ or (radiopharmaceutical$ adj2 treat$)).mp.	1696
3	(("90" adj2 y$ adj2 DOTA$) or ("90" adj2 y$ adj2 octreot$) or ("90" adj2 y$ adj2 lanreot$) or (90Y$-octreot$ or 90Y$-DOTA$ or 90Y$-lanreot$) or (y$90-octreot$ or y$90-DOTA$ or y$90-lanreot$)).mp.	285
4	(("90" adj2 y$ adj2 edotre$) or 90Y$-edotre$ or y$90-edotre$ or ("90" adj2 y$ adj2 Dode$) or 90Y$-SMT$ or Y$90-SMT$ or ("90" adj2 y$ adj2 SMT$) or y$90-dode$).mp.	99
5	(("111" adj2 (in or indium) adj2 octreot$) or 111In-octreot$ or 111Indium-octreot$ or in111-octreot$ or indium111-octreot$).mp.	409
6	(("111" adj2 in adj2 DOTA$) or ("111" adj2 indium adj2 DOTA$)).mp.	133
7	(111in-DOTA$ or 111indium-DOTA$ or in111-DOTA$ or indium111-DOTA$).mp.	83
8	(("111" adj2 in adj2 pentetr$) or ("111" adj2 indium adj2 pentetr$) or 111In-pentetr$ or 111Indium-pentetr$ or In111-pentetr$ or Indium111-pentetr$ or neuroendmed$).mp.	356
9	(("177" adj2 lu$ adj2 octreot$) or 177lu-octreot$ or 177lutetium-octreot$ or lutetium177-octreot$ or lu177-octreot$ or ("177" adj2 lu$ adj2 DOTA$) or 177lu-DOTA$ or 177lutetium-DOTA$ or lu177-DOTA$ or lutetium177-DOTA$ or DOTA, TYR3$).mp.	153
10	(131-I-mibg or 131-I-meta$ or 131I-mibg or 131I-meta$ or I131-mibg or I131-meta$ or I-131-mibg or I-131-meta$).mp.	988
11	(I-131-iobeng$ or I131-iobeng$ or ("131" adj2 iobeng$) or ("131" adj2 I adj2 mibg) or ("131" adj2 I adj2 meta$)).mp.	447
12	or/1-11	13561
13	exp Neuroendocrine Tumors/	115251
14	(neuroendocrine adj2 (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)).mp.	7618
15	exp Carcinoid Tumor/	10229
16	(insulinoma or gastrinoma$ or glucagonoma$ or vasoactive intestinal peptideoma$ or VIPoma$).mp.	7405
17	(PPoma$ or somatostatinoma$ or ACTHoma$ or parathyroid hormone-related peptide tumo?r$ or PTH-rp secreting tumo?r$).mp.	401
18	((pancreatic adj1 endocrine tumo?r$) or pancreatic islet cell tumo?r$ or GEP-Net$ or NE-GEP$ or NET$).mp.	316016
19	(Multiple endocrine neoplasia$ or (neuroblastoma$ or ph?eochromocytoma$ or paraganglioma$)).mp.	54275
20	(appendiceal endocrine adj (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)).mp.	2
21	(goblet cell adj (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)).mp.	9
22	(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.	1477178
23	or/13-21	472071
24	(12 and 23) not 22	1743
25	limit 24 to (english language and humans and yr="1998 -Current")	859

Note: The Working Group decided to add medullary thyroid cancer in the literature search (Jan 21, 2011)

	((medullary adj2 thyroid adj2 (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)) or MTC).mp.	4616
	limit it to (English language and humans and yr="1998 - 2010")	66

After removing the duplicate citations, there are 859+37 = 896 hits.

Appendix 3. EMBASE searching for neuroendocrine cancer.

Database(s): **EMBASE** 1996 to 2010 Week 43 Search Strategy:

#	Searches	Results
1	((radionuclide$ adj2 therap$) or (radioisotope$ adj2 therap$) or salvage therap$ or (radiopharmaceutical$ adj2 therap$) or PRRT$).mp.	11601
2	((radionuclide$ adj2 treat$) or (radioisotope$ adj2 treat$) or salvage treat$ or (radiopharmaceutical$ adj2 treat$)).mp.	4081
3	(("90" adj2 y$ adj2 DOTA$) or ("90" adj2 y$ adj2 octreot$) or ("90" adj2 y$ adj2 lanreot$) or (90Y$-octreot$ or 90Y$-DOTA$ or 90Y$-lanreot$) or (y$90-octreot$ or y$90-DOTA$ or y$90-lanreot$)).mp.	425
4	(("90" adj2 y$ adj2 edotre$) or 90Y$-edotre$ or y$90-edotre$ or ("90" adj2 y$ adj2 Dode$) or 90Y$-SMT$ or Y$90-SMT$ or ("90" adj2 y$ adj2 SMT$) or y$90-dode$).mp.	98
5	(("111" adj2 (in or indium) adj2 octreot$) or 111In-octreot$ or 111Indium-octreot$ or in111-octreot$ or indium111-octreot$).mp.	413
6	(("111" adj2 in adj2 DOTA$) or ("111" adj2 indium adj2 DOTA$)).mp.	54
7	(111in-DOTA$ or 111indium-DOTA$ or in111-DOTA$ or indium111-DOTA$).mp.	175
8	(("111" adj2 in adj2 pentetr$) or ("111" adj2 indium adj2 pentetr$) or 111In-pentetr$ or 111Indium-pentetr$ or In111-pentetr$ or Indium111-pentetr$ or neuroendmed$).mp.	1428
9	(("177" adj2 lu$ adj2 octreot$) or 177lu-octreot$ or 177lutetium-octreot$ or lutetium177-octreot$ or lu177-octreot$ or ("177" adj2 lu$ adj2 DOTA$) or 177lu-DOTA$ or 177lutetium-DOTA$ or lu177-DOTA$ or lutetium177-DOTA$ or DOTA, TYR3$).mp.	301
10	(131-I-mibg or 131-I-meta$ or 131I-mibg or 131I-meta$ or I131-mibg or I131-meta$ or I-131-mibg or I-131-meta$).mp.	608
11	(I-131-iobeng$ or I131-iobeng$ or ("131" adj2 iobeng$) or ("131" adj2 I adj2 mibg) or ("131" adj2 I adj2 meta$)).mp.	145
12	or/1-11	16612
13	exp neuroendocrine tumor/	21287
14	(neuroendocrine adj2 (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)).mp.	8440
15	exp carcinoid/	6239
16	(insulinoma or gastrinoma$ or glucagonoma$ or vasoactive intestinal peptideoma$ or VIPoma$).mp.	4747
17	(PPoma$ or somatostatinoma$ or ACTHoma$ or parathyroid hormone-related peptide tumo?r$ or PTH-rp secreting tumo?r$).mp.	336
18	((pancreatic adj1 endocrine tumo?r$) or pancreatic islet cell tumo?r$ or GEP-Net$ or NE-GEP$ or NET$).mp.	261448
19	(Multiple endocrine neoplasia$ or (neuroblastoma$ or ph?eochromocytoma$ or paraganglioma$)).mp.	32999
20	(appendi$ endocrine adj (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)).mp.	2
21	(goblet cell adj (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)).mp.	429
22	or/13-21	320360
23	(editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/	1212603
24	(12 and 22) not 23	2179
25	limit 24 to (human and english language and yr="1998 -Current")	1512

Note: The Working Group decided to add medullary thyroid cancer in the literature search (Jan 21, 2011):
((medullary adj2 thyroid adj2 (cancer$ or neoplasm$ or carcinom$ or maligan$ or tumo?r$)) or MTC).mp. 4297
limit it to (English language and humans and yr="1998 - 2010") 179
After removing the duplicate citations, there are 1512+96 = 1608 hits.

Evidence-Based Series 12-13: Section 3

Radionuclide Therapy for Neuroendocrine Malignancies: Evidence-based Series Development Methods and External Review Process

K.Y. Gulenchyn, X. Yao, S.L. Asa, S. Singh, C. Law,
and members of the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel

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

Report Date: August 15, 2011

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) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as Guideline Development Groups (GDGs) called together for a specific topic, all mandated to develop the PEBC products. These groups are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel and Working Group (Appendix 1 in Section 2) of the CCO PEBC and CCO Clinical Program. The series is a convenient and up-to-date source of the best available evidence on the role of radionuclide therapy in neuroendocrine cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Radionuclide Therapy for Neuroendocrine Tumours Expert Panel Conference

On March 4, 2011, the draft guideline was presented to members of the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel. This guideline contained draft recommendations that had been crafted by the Working Group. There was no strong disagreement regarding these draft recommendations or evidentiary base. It was suggested that several recommendations be reworded into more action-oriented language, and that the order and classification of the recommendations and qualifying statements be changed somewhat to highlight the most important issues.

Some members of the Expert Panel did express concern with respect to the study selection criteria, specifically the sample size limits (i.e., ≥30 for prospective studies and ≥100 for retrospective studies). There was concern that retrospective studies with sample sizes of less than 100 may provide some valuable information not currently included.

Based on the Expert Panel's feedback, the Working Group members revised the recommendations in the guideline and the conclusion of the evidentiary base. As the time available for the completion of this guideline was limited, the Working Group decided to submit the updated draft to the Report Approval Panel (RAP) for review. At the same time, retrospective studies with sample size between 30 and 100 would be reviewed and the results provided in an appendix after RAP review.

PEBC Director's Review

Following the presentation of this EBS draft report for Expert Panel review, the report was reviewed and approved by the director of the PEBC, Dr. Melissa Brouwers, with expertise in methodologic issues. Key issues raised by the director included:

- Reorganizing the key evidence orders in Section 1.
- Reorganizing the sentences under Synthesizing the Evidence in Section 2.
- Adding an overall summative statement under Study Quality in Section 2.
- Changing the axis labels in Figures 2-3 in Section 2.

In response to the RAP review feedback, all the raised points were revised by the Working Group.

Retrospective Studies with Sample Size between 30 and 100

Seven retrospective studies with sample size between 30 and 100 were found and listed in Appendix 1. All the studies investigated the efficacy of ^{131}I-MIBG. Since the retrospective study design is an inappropriate study design for testing the effect of radionuclide therapy in neuroendocrine cancer patients and has a greater potential for bias and thus can be more difficult to interpret than the prospective studies, the Working Group members decided to clarify this point in study selection criteria in Section 2 and continued to exclude these studies from this guideline.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the guideline authors circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the guideline authors.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review May 3, 2011)

QUESTIONS

1. Among eight commonly used and studied therapeutic radiopharmaceuticals described in Table 1 below, which one is most effective in improving clinical outcomes (i.e., tumour response, duration of tumour response, overall survival [OS] time/rate, progression free survival [PFS] time/rate, biochemical response, and quality of life) in patients with different types of neuroendocrine malignancies?
2. What are the toxicities for each therapeutic radiopharmaceutical?

Table 1. Radiopharmaceuticals considered by this practice guideline.

Name	Alternate name
^{111}In-DTPAOC	[^{111}In-DTPA^{0}]octreotide, ^{111}In-DTPA-D-Phe-octreotide, ^{111}In-pentetreotide
^{111}In-DOTATATE	^{111}In -DOTA-TYR^{3}-octreotate, ^{111}In-octreotate
^{90}Y-DOTATOC	^{90}Y-DOTA-TYR^{3}-octreotide, ^{90}Y-SMT487, ^{90}Y-edotreotide
^{90}Y-DOTALAN	^{90}Y-DOTA-lanreotide
^{90}Y-DOTATATE	^{90}Y-DOTA-TYR^{3}-octreotate, ^{90}Y-octreotate
^{177}Lu-DOTATOC	^{177}Lu-DOTA-TYR^{3}-octreotide, ^{177}Lu-octreotide
^{177}Lu-DOTATATE	^{177}Lu-DOTA-TYR^{3}-octreotate, ^{177}Lu-octreotate
^{131}I-MIBG	^{131}I-metaiodobenzylguanidine, ^{131}I-iobenguane

TARGET POPULATION

These recommendations apply to neuroendocrine cancer patients who are inoperable, or have residual disease following surgery or other ablative therapy, or have metastases.

INTENDED USERS

This guideline is intended to be used by nuclear medicine physicians, medical oncologists, surgeons, and pathologists who are involved in the treatment of the above-targeted patients.

INTRODUCTION

Neuroendocrine tumours (NETs) constitute a heterogeneous group of neoplasms; they include epithelial neuroendocrine carcinomas originating in multiple sites throughout the body as well as tumours of modified neurons arising in sympathetic or parasympathetic ganglia and the adrenal medulla (1,2). The latter express tyrosine hydroxylase to synthesize dopamine, and therefore readily take up ^{131}I- and ^{123}I-MIBG; however, the former express somatostatin receptors as a distinguishing feature and are amenable to ablation with radiolabeled somatostatin analogues (1,2). Although therapy with both MIBG and radiolabeled somatostatin analogues has been provided in Ontario, it has not been made broadly available; barriers to access have resulted in out-of-country requests. A systematic review was conducted to inform recommendations for the selection of agents for therapy and to inform the development of criteria for access to radionuclide therapies for NET patients in Ontario. The details of the method and results of this systematic review are shown in Section 2. There are no randomized controlled trials (RCTs) examining the effectiveness of any of the peptide receptor radionuclide therapy (PRRT) agents or ^{131}I-MIBG in the treatment of neuroendocrine cancer patients. Trials have not been conducted to compare either PRRT or ^{131}I-MIBG with placebo, systemic therapy, tumour debulking treatment, or long-acting somatostatin analogues. Furthermore, no trials have been conducted to make direct comparisons between or among the eight agents reviewed.

RECOMMENDATIONS AND KEY EVIDENCE

The Expert Panel and the Working Group offer the following recommendations based on the evidence reviewed:

- PRRT appears to be an acceptable option in adult patients with neuroendocrine cancer who are inoperable, have residual disease following surgery or other ablative therapy, or have metastases.
- ^{131}I-MIBG might be effective for malignant neuroblastoma, paraganglioma, or pheochromocytoma, but there is insufficient evidence to suggest its efficacy for adult neuroendocrine carcinoma patients.
- Treatment with PRRT in Ontario should be conducted as part of one or more RCTs, or large comparative clinical trials if an RCT is not feasible, under the authority of a Clinical Trials Agreement, to clarify the effects of PRRT.

Qualifying Statements

- There is limited evidence, based on a historical comparison of studies from a single centre (see Key Evidence below), that ^{177}Lu-DOTATATE may be associated with greater OS, PFS, and overall response rate (defined as the sum of complete response, partial response, and minor response rates) compared with ^{90}Y-DOTATOC or ^{111}In-DTPAOC. Therefore, ^{177}Lu-DOTATATE would be an appropriate agent to include in the future clinical trials described above.
- Prior to the administration of therapy, the tumours from NET patients that are to

receive PRRT or ^{131}I-MIBG should demonstrate positive uptake of the related diagnostic agent.
- PRRT is relatively safe and well tolerated with renal protection using lysine and arginine amino acid solution in adult malignant NET patients. However, with ^{131}I-MIBG therapy, the haematological toxicity, severe infections, and secondary malignancies possible afterwards need to be considered.
- A recommendation cannot be made for or against the use of PRRT in early-stage NET patients as there is no relevant evidence.

Key Evidence

Peptide Receptor Radionuclide Therapy

- Fifteen prospective single-arm articles (3-17) and one prospective comparative study (18) met the study selection criteria; of the nine published after 2005, all investigated the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, or ^{177}Lu-DOTATATE (9-17). The total sample size was 1179. All the patient tumours showed a higher or same uptake on octreoscan than on liver uptake before PRRT. All but one study (12) reported the overall response rate as determined by three different imaging criteria in a variety of stage III-IV NET subgroups. Across all agents, overall response rates ranged from 5% to 75% in various tumour subgroups, with wide 95% confidence intervals (CI) (See Figure 2 in Section 2).
- Three studies were conducted in the same clinical centre to investigate the effects of ^{111}In-DTPAOC, ^{90}Y-DOTATOC, and ^{177}Lu-DOTATATE at different time periods (5,10,13). The median OS and PFS time was 37 and 14 months, respectively, for ^{90}Y-DOTATOC at five-year follow-up (10); and 46 and 33 months, respectively, for ^{177}Lu-DOTATATE at four years (14). The overall response rate was 18% (CI, 6-30%) for patients with progressive stage III-IV NET treated with ^{111}In-DTPAOC, 21% (CI, 11-31%) for patients with stage III-IV GEP-NET disease treated with ^{90}Y-DOTATOC, and 46% (CI, 40-52%) for patients with stage IV GEP-NET disease treated with ^{177}Lu-DOTATATE.
- Eight of the 16 articles reported survival outcomes, with six reporting median OS times ranging from 15 to 46 months for various stage III-IV NET subgroups (10,11,13,15-17). There was no significant difference in OS time between the intervention (14 patients treated with ^{111}In-DTPAOC and five patients treated with ^{131}I-MIBG) and control arm in the unique comparative trial (8).
- Of the fifteen articles that reported on toxicity, 11 specified one of two criteria used for grading toxicity. Nausea and vomiting were common during therapy. The severe toxicities included the following: For ^{111}In-DTPAOC, 8% of patients developed myelodysplastic syndrome (MDS) and/or leukemia in one study (5); for ^{90}Y-DOTATOC, 0.9-3.4% of patients developed grade 4 renal toxicity in three studies (9-11), with 2% of patients developing MDS in one study (10); for ^{90}Y-DOTALAN, no severe toxicity was found in one study (6); for ^{90}Y-DOTATATE, 30% of patients developed grade 2 renal toxicity at two years in one study (16); for ^{177}Lu-DOTATATE, 0.6% of patients developed hepatic insufficiency, 0.8% developed MDS, and 0.4% developed renal insufficiency in one study (13). For studies investigating the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, and ^{177}Lu-DOTATATE, lysine and arginine amino acid solution was infused to protect kidney function.

^{131}I-MIBG Therapy

- Six prospective single-arm, one retrospective comparative, and one retrospective single-arm study examining the effectiveness of ^{131}I-MIBG were eligible; the total sample size was 612. All the patients showed at least one lesion was positive on the

^{123}I-MIBG or ^{131}I-MIBG scintigraphy. The overall tumour response rate on imaging by various imaging criteria ranged from 32% to 75% for stage III-IV paediatric neuroblastoma patients with median age 2.0-6.6 years old (19-23) and was 26% for adult and stage III-IV NET patients (24) (including 22 neuroblastomas, 10 pheochromocytomas, three paragangliomas, six medullary thyroid carcinomas, and four carcinoids) and 27% for patients with stage IV paraganglioma or pheochromocytoma (25) (See Figure 3 in Section 2).

- The Sywak et al study was the unique comparative study for comparing standard therapies alone with standard therapies plus ^{131}I-MIBG in stage IV patients with midgut carcinoid (26). The OS rate was 63% (CI, 47-75%) in the intervention group and 47% (CI, 34-59%) in the control group at five years without statistical significance (p=0.10).
- Of seven studies reporting on toxicity, three used different criteria, and four studies did not specify the criteria for toxicity grading. Hematologic toxicities were the main severe side effects. Forty-three percent of patients had bone marrow replacement (BMR), and one patient developed secondary leukemia in one study (19). Five percent of patients in one study (20) and 2% of patients in another study (22) developed leukemia or MDS. In a retrospective study, five (4%) three to five-year-old neuroblastoma patients developed secondary malignancies after ^{131}I-MIBG therapy either as part of first-line therapy or as salvage therapy for resistant or recurrent disease: one acute nonlymphoblastic leukemia at one and a half years, one chronic myelomonocytic leukemia at four years, one malignant schwannoma at seven years, one rhabdomyosarcoma at 14 years, and one angiomatoid malignant fibrous histiocytoma at 10 years after ^{131}I-MIBG (21). In a fifth study, 39% of patients needed autologous BMR, and 9% of patients died (23) where ^{131}I-MIBG was utilized as the first-line treatment. Forty-one percent of patients had grade 2-3 hematologic toxicities in a sixth study (24). After an accumulative dose of at least 63.3 gigabecquerel (GBq) ^{131}I-MIBG therapy, 4% of patients who did not have prior radiation or chemotherapy developed MDS and acute myeloid leukemia at two and five years, respectively, in the seventh study (25). In addition, 4% of patients in that same study developed acute respiratory distress syndrome, 4% developed bronchiolitis obliterans organizing pneumonia, and 2% had a pulmonary embolism.

Treatment Alternatives

Somatostatin analogs have been proved to be more effective than placebo in the control of tumour growth in patients with metastatic midgut NETs in an RCT (27).

Recently, investigators of two studies have reported positive results in the use of biologic agents for the treatment of malignant pancreatic NETs: one was the tyrosine kinase inhibitor sunitinib and the other was the mTOR (mammalian target of rapamycin) inhibitor, everolimus (28,29). Both trials were phase III, multicentre, double-blind, randomized, placebo-controlled trials with sufficient numbers of patients to yield clear statistical results. Sunitinib, as compared with placebo, caused more than a doubling in PFS (11.4 versus [vs.] 5.5 months, respectively, $p<0.001$). Everolimus caused a 65% reduction in the estimated risk of progression (PFS of 11.0 months for everolimus vs. 4.6 months for placebo, $p<0.001$).

FUTURE RESEARCH

The recent publications that report positive results with the biological agents of sunitinib, everolimus, and octreotide long-active release (LAR), particularly with regard to PRRT, raise many important questions that could be the subject of further

investigation. Should these drugs be used in combination with somatostatin analog therapy? Should these drugs be used before, after, or in combination with PRRT? Can these drugs be used alone or in combination with PRRT as adjuvant or neoadjuvant therapy (with surgery)?

Furthermore, the use of PRRT early in the treatment of NET patients (i.e., before maximal medical treatment) has not been explored and should be an option for further study in Ontario.

The development of a standardized program for the assessment, treatment, and follow-up of NET patients in Ontario is essential to ensure the existence of an appropriate infrastructure for the evaluation of promising new therapies that would provide patients suffering from NETs with high-quality, evidence-based care.

Methods

Targeted Peer Review: During the guideline development process, 11 targeted peer reviewers from the world considered to be clinical and/or methodological experts on the topic were identified by the guideline authors. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on April 29, 2011. Follow-up reminders were sent at two weeks and at four weeks. All the targeted peer reviewers were required to complete the conflict of interest form.

Professional Consultation: 104 potential participants were identified by the guideline authors. Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on May 3, 2011. Two follow-up reminders were sent on May 19 and May 31, 2011.

Results

Targeted Peer Review: Responses were received from three of four reviewers: K. Oberg from Sweden, R. Lebtahi from France, and B. Wiedenmann from Germany. Key results of the feedback survey are summarized in Table 1. Summary of written comments by targeted peer reviewers and modifications/actions/responses taken are summarized in Table 2.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (n=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	1	1	1
2. Rate the guideline presentation.	0	1	0	1	1
3. Rate the guideline recommendations.	0	1	0	1	1

4. Rate the completeness of reporting.	0	1	0	1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	1	0	1	1
6. Rate the overall quality of the guideline report.	0	1	0	1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	1	0	0	1	1
8. I would recommend this guideline for use in practice.	1	0	0	1	1
9. What are the barriers or enablers to the implementation of this guideline report?	One reviewer commented that randomized clinical trials are not yet available, and comparison between the various treatments is lacking. Therefore, no treatment cycle dose or optimal cycle interval or optimal cumulative dose can be given. The development of a standardized program for the treatment, and follow-up of NET patients are needed.				

Table 2. Summary of written comments by targeted peer reviewers and modifications, actions, or responses regarding written comments.

Summary of written comments	Modifications, actions, or responses
1. The recommendations are based on current information, where we are lacking prospective randomized trials (RCTs). With that as a background, the recommendations are clinically sound. I think this document provides sufficient information for decision on a program. Maybe a more in-depth discussion about schedules and isotopes might have been helpful.	Since there is limited evidence of schedules and isotopes from the included articles (see Table 3. *Administered dose and treatment schema* in Section 2) and a wide range among different radiopharmaceuticals, further discussion about schedules and isotopes will not be very meaningful.
2. The guideline is complete and very well organized. Recommendations are consistent with the literature and clearly stated. Very full report of literature results are obtained and analyzed. The limits of reported studies are listed: the absence of RCTs, the administered doses and dosing schemes differ, patient selection and tumour characteristics, differences in tumour response criteria. Two ongoing trials (from the NCI	The first ongoing trial will enrol 35 patients. There was a publication with a sample size of 17, and so it was excluded from this guideline (3). In addition, the investigators stated that only patients with histologically or cytologically confirmed malignant neoplasm would be recruited in their trial. Four of these 17 patients in this paper had pinealoblastoma, anaplastic astrocytoma, medulloblastoma, and choroid plexus carcinoma that did not belong to NETs. As this ongoing trial is unlikely to enrol ≥30 patients with NETs, it will be not added in the ongoing trial table. For the second ongoing trial, the investigator would like to enrol five patients according to their protocol on: http://clinicaltrials.gov/show/NCT00815620, which

clinical trials database) for PRRT need to be added: (1). Phase I Study of Yttrium Y 90-DOTA-tyr3-Octreotide in Children With Advanced or Refractory Somatostatin Receptor-Positive Tumors (Protocol IDs: UIHC-200008086, NCI-V02-1710, NCT00049023, 200008086); (2). Best Therapy for Patients With Neuroendocrine Tumors	met our exclusion criteria, and so it was not shown in our ongoing trial list. However, on the site: http://www.cancer.gov/clinicaltrials/search/view?cdrid=631952&version=HealthProfessional&protocolsearchid=8986201, the same trial plans to enrol 210 patients. For this reason, it has been added to Table 9a (ongoing trials) now.
3. The existing literature in the field of PRRT is extremely well elaborated in this systemic review by a multidisciplinary expert panel. Based on the excellent review of the literature, it is recommended to publish the data in a high ranking journal. The presented data do not represent in the opinion of the reviewer actual guidelines in comparison to existing national as well as international guidelines. In this context, it would be helpful to learn more about the expertise of the panel members in the field of GEP-NETs. The reviewer is left with the impression that attempts have been made to develop a study protocol for a phase II trial by comparing the best established radiology and 177 Lu-DOTATATE with the non-established and questionable radiology and MIBG in GEP-NETs. In case that this proposal would represent the submission of a study protocol for PRRT, however, a detailed protocol is missing. Only some references are given for other treatment modalities incl. larger robust RCT (e.g., sunitinib, everolimus, etc,) whereas important refs. are missing (e.g. Moertel et al. NEJM, 1989 or Strossberg et al., Cancer 2010). Furthermore, these alternative treatment modalities	There was no attempt made to compare ^{177}Lu-DOTATATE with ^{131}I-MIBG in Section 1. To avoid misleading the readers, the second and third recommendations have been switched, and one possible future research example is shown in the second recommendation. Further research of PRRT in Ontario is beyond the scope of this guideline. Thus, a detailed protocol is not needed. The Moertel 1989 study in *NEJM* investigated the effect of recombinant leukocyte A interferon in a single-arm study with n=27; the Strossberg 2010 study in *Cancer* was a retrospective single-arm study and focused on chemotherapy with n=30. Mentioning these two studies in this guideline would not be helpful. Analysis of the toxicities, costs, health benefits, and risks of the alternative treatment modalities is beyond the scope of this guideline. There is a subsection Treatment Alternatives in Section 1. PRRT seems to be an acceptable *option* for adult patients with advanced NET. Additional well-designed research for the treatment of NET patients is needed to determine whether it is the *best* treatment option.

are not discussed with regards to toxicities, costs, health benefits and risks. The reader is left with the impression that PRRT represents the only valid treatment option in GEP-NET.	
4. The presented data need to be expanded with regards to the existing TNM and grading classification (e.g., WHO 2010), primary location (leading also to different response rates), extent of metastatic liver involvement, diagnostic use of MIBG in GEP-NET, etc.	Had the published literature consistently identified the different primary location type of NETs, and applied TNM and grading classifications, this data would have been included in the review. However, the present limited evidence does not provide the needed data. The diagnostic issue is beyond the scope of this guideline.
5. It is unclear to the reviewer how the guideline development process took place considering a rather biased, unfinished protocol. It is also unclear how decisions for the use of MIBG were sampled considering the lack of data in GEP-NETs.	Please see the response for Comment 3.
6. Missing are references to a prospective multicenter international trial currently in process comparing 177 Lu-DOTATATE with unlabeled octreotide in a Phase III setting (Rotterdam).	The reviewer provided us with a link for an ongoing RCT that was registered at the Netherland Clinical Trial Web site (http://www.trialregister.nl/trialreg). It has been added to the ongoing trials, Table 9a, and to the Discussion in Section 2. The European Clinical Trial Register (https://www.clinicaltrialsregister.eu/) was searched on June 1, 2011, and another two ongoing trials about PRRT in NET patients were found and added to Table 9a.

Professional Consultation: Twenty-six of 104 (25%) responses were received. The key results of the feedback survey are summarized in Table 3. The comments from the professional consultants and the Working Group modifications/actions taken in response are summarized in Table 4.

Table 3. Responses to four items on the professional consultation survey.

Question	Number (n=26)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	1	3	14	8
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	3	2	16	5

3. I would recommend this guideline for use in practice.	0	3	3	14	6
4. What are the barriers or enablers to the implementation of this guideline report?	Availability of radionuclide therapy, funding, database infrastructure, and easy access in different centers. A significant barrier would be lack of high-powered evidence in the use of radionuclide therapy and how this therapy is to be used in conjunction with available therapies. Octreotide scans at my center can have a 6 to 8 week wait which requires extensive explanation to patients about these delays. Patients feel an urgency that is difficult to overcome with any explanations. A relatively small number of knowledgeable practitioners, therefore, a challenge to engage others who see these patients to be aware and make use of guideline.				

Table 4. Summary of written comments by professional consultants and modifications/actions/responses regarding written comments.

Summary of written comments	Modifications, actions, or responses
1. PRRT is deemed an acceptable option but it is not an option as it has to be used as part of a RCT or league comparative trial "to clarify the effect of PRRT". If the effects were not clear, then how could the expert panel write it "appears to be an acceptable option" and what specifically needs to be clarified. The response rate data in Fig 2 & 3 would seem sufficient to indicate efficacy for PRRT and 131I- M1BG!!	PRRT is gradually used in advanced NET patients worldwide. However, there are a lot of unknown issues about further effect of PRRT (please see Further Researches in Section 1). Thus, further RCTs or large comparative studies are required to figure out these issues. To clarify this point, some examples are added in Recommendations in Section 1 and in Conclusion part in Section 2.
2. The literature pertaining to the use of each individual agent for PRRT is sparse. Furthermore, the level of evidence is poor and the heterogeneity of the patients with regard to site of origin, varying diagnostic techniques, previous therapies prior to PRRT, and differences in follow-up and response criteria make comparison of the available studies extremely difficult. While PRRT is extensively used in all of the high volume centres with advanced disease. However, I would agree that Lueticium-177 holds the most promise based on the case series from Kwekkeboom et al from Rotterdam as well as my personal observations from visiting the Neuroendocrine Center of Excellence at the University of Upsula where they presented some of their unpublished results. I believe it is worthwhile to pursue this treatment option for our patients in Ontario, I would urge the CCO as well as the members of the expert panel to study the efficacy of this treatment in a prospective fashion. In doing so,	As with the response to Comment 1, some examples are added to the Recommendations in Section 1 and the Conclusion in Section 2.

there is an opportunity here to contribute a seminal article in the treatment of neuron-endocrine tumour patients. Thank you for the opportunity to participate in this review.	
3. Future research section: "should these drugs be used in combination with somatostatin analog therapy?" LAR octreotide is itself a somatostatin analog.	This sentence has been deleted.
4. This Guideline summarizes the current state of radionuclide treatment of NETs. As stated very clearly in the guideline that lack of RCTs and the incredible heterogeneity of trials and study populations make it impossible to draw any firm conclusions about the efficacy of these treatments. The guideline, though its use of an exhaustive systematic review, confirms the lack of evidence for the use of these treatments, and the great need for either RCTs or very large comparative studies. Minor thoughts: 1) In the summary writing of other therapies, the authors should probably state that for the Sutent trail and RADIANT3 that these trials focused on pancreatic NETs exclusively, and may wish to include RADIANT2. 2) Might be helpful in the executive summary to mention the large ongoing trials that may help clarify efficacy and toxicity further.	Regarding the reviewer's two minor thoughts: 1). The Raymond 2011 and Yao 2011 articles have been added to Section 2. The RADIANT2 RCT, comparing everolimus plus octreotide LAR with placebo plus octreotide LAR in patients with advanced NET, has not been published as a full text, and so it will not be added in this guideline. 2). The largest single-arm ongoing trial just published its main outcomes in June 2011. Since its clinical reports do not impact the recommendations in this guideline, the guideline authors have decided not to update the literature search now, and its information is added to the Discussion in Section 2.
5. The treatment and care of patients with NET's will be constantly evolving over the next several years due to increased survival directly related to the current therapies offered in Canada. Education among the health care providers in Canada is priority so patients are able to access the appropriate treatment. The focus of the documentation reviewed is on the current results of trials and the guidelines for treatment options. It fails to address the ongoing management of patients post isotope therapy. There must be SHARED care for our patients with NET's. This has been a major barrier for our patients. It is my hope with the development of these guidelines in the recommendation section it is clearly stated that care is shared between the referring physician and the centre providing the radioisotope therapy. There appears to be reluctant or the referring physicians to accept the patient back to their care once isotope therapy is no longer effective. Development of these guidelines is a step in	These comments are important, but they are beyond the scope of this guideline to address. Consideration will be given by relevant organizations such as the Ontario Ministry of Health and Long-Term Care when making decisions about how to apply PRRT for NET patients in Ontario in the future.

the right direction. They will help to ensure the NET population of patients have access to the best possible care in Canada. It is my hope that the guidelines will be incorporated as part of the curriculum for the upcoming medical students and present NET's as an interesting dynamic disease that will be constantly pushing new frontiers in the medical world.	
6. A standardized program for radioisotope-labelled peptides will likely work if it all such treatments are done in tertiary referral centers.	As with Comment 5, this topic is beyond the scope of this guideline.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel and the Working Group.

UPDATES

Updates of this report will be conducted at three years or at any time as new important evidence informing the question of interest emerges and would change the recommendations.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Expert Panel members, and internal and targeted external reviewers were asked to disclose potential conflicts of interest. Three guideline authors declared they had no conflicts. Two others (S. Singh and C. Law) declared conflicts and reported receiving more than $5000 in a single year from consulting fees, honoraria, and/or other support from Novartis and Pfizer pharmaceutical companies. Both these authors also declared that they had received research grant support from Novartis.

For the Expert Panel, seven members declared they had no conflicts of interest, and two (T. Besanger and R. Reid) declared conflicts. TB reported receiving employment income from a previous employer, Molecular Insight Pharmaceuticals, a clinical developer of ^{90}Y-DOTATOC and ^{131}I-MIBG. RR reported receiving more than $5000 in a single year for travel expenses and research funding (now completed) from Novartis for his department for database development.

The PEBC Director (M. Browers) and the PEBC Assistant Director (H. Messersmith) declared that they had no COI.

For the targeted external reviewers, two declared they had no COI, and one (R. Lebtahi) declared conflicts. RL was the co-author in the European neuroendocrine tumour society (ENETS) guideline (4), and he will be a principal investigator for a multicentre trial about ^{111}In-DTPAOC therapy in front of curative intent after complete resection of liver metastases in patients with NETs in France at the end of 2011 year.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.

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Appendix 1. Retrospective studies with sample size between 30 and 100.

Peptide receptor radionuclide therapy
No studies were found.
^{131}I-MIBG therapy
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