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# The therapeutic efficacy of ^{177}Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors

## A meta-analysis

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**Abstract**

**Background:** Somatostatin analog therapies showed great potential for patients suffering advanced neuroendocrine tumors (NETs). This study was aimed to evaluate the therapeutic efficacy of ^{177}Lu-DOTATATE/DOTATOC (^{177}Lu-octreotate/octreotide) peptide receptor radionuclide therapy (PRRT) in advanced or inoperable NETs patients.

**Methods:** Pubmed, Web of Science, Embase and Cochrane Library were searched from 1950 to April 2019. Eligible studies should include randomized or nonrandomized controlled trials (RCTs)-based investigations of ^{177}Lu-octreotate/octreotide PRRT for NETs. All these studies were assessed with Response Evaluation Criteria in Solid Tumors (RECIST), RECIST 1.1, Southwest Oncology Group (SWOG) criteria or World Health Organization (WHO) criteria. Disease response rates (DRRs) and disease control rates (DCRs) were calculated according to each response criteria group. DRRs were defined as the percentages of patients with complete response (CR) + partial response (PR), while DCRs represented the percentages of patients with CR+ PR+ stable disease (SD). The pooled proportions were calculated with either a fixed-effects model or a random-effects model depending on the test for heterogeneity.

**Results:** A total of 22 studies (1758 patients) were included in this meta-analysis: 8 studies with 478 patients met RECIST criteria, 10 studies with 1127 patients met RECIST 1.1 criteria, 5 studies with 459 patients met SWOG criteria, and 1 study with 40 patients met WHO criteria, and among these articles 1 study met both RECIST and RECIST 1.1 criteria and 1 met both RECIST 1.1 and SWOG criteria. The pooled DRRs were 33.0% (95% CI: 25.0%-42.0%, $I^2 = 65\%$), 35.0% (95% CI: 26.0%-45.0%, $I^2 = 91\%$) and 25.0% (95% CI: 14.0%-36.0%, $I^2 = 84\%$) according to RECIST, RECIST 1.1 and SWOG criteria, respectively. The pooled DCRs were 79.0% (95% CI: 75.0%-83.0%, $I^2 = 97\%$), 83.0% (95% CI: 78.0%-88.0%, $I^2 = 0$) and 82.0% (95% CI: 75.0%-89.0%, $I^2 = 91\%$), respectively.

**Conclusion:** In advanced NETs patients, DRRs and DCRs were significantly elevated after initial treatment with ^{177}Lu-DOTATATE PRRT, which shows that this treatment would be beneficial and promising for advanced or inoperable NETs patients.

**Abbreviations:** ^{177}Lu-DOTATATE/DOTATOC = ^{177}Lu-octreotate/octreotide, DCRs = disease control rates, DRRs = disease response rates, NETs = neuroendocrine tumors, PFS = progression free survival, PRISMA = preferred reporting items for systematic reviews and meta-analysis, PRRT = peptide receptor radionuclide therapy, RECIST = response evaluation criteria in solid tumors, SWOG = Southwest Oncology Group, WHO = World Health Organization.

**Keywords:** ^{177}Lu-DOTATATE/DOTATOC, advanced neuroendocrine tumors, meta-analysis, neuroimaging, positron emission tomography

## 1. Introduction

Heterogeneity and slow-growth are the main characteristics of neuroendocrine tumors (NETs).[1,2] They used to be defined as rare malignancies, but in the past 3 decades, the prevalence of NETs raised approximately 5 folds in the United States.[3] A study in 2008 based on the data of Surveillance, Epidemiology, and End Results (SEER) program registries showed that the incidence of NETs elevated from 1.09/100000 to 5.25/100000 from 1973 to 2005.[4] As a result, the perception and treatment of NETs drew oncologists and researchers' great attention in the past 15 years.[5] As for NETs patients with operable and localized focus, the first choice is surgical resection. However, tumors of this type are usually diagnosed in the late-phase due to the slow-growing nature and the nonspecific signs which make surgical resection impossible.[6]

Most NETs cell membrane overexpressed somatostatin receptor which was emphasized as the target for peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin.[7] In 1990s, radiolabeled somatostatin analogeus ^{111}In-octreotide, was first applied in NETs therapy.[8] Since then, more radionuclide tracers have been used for NETs treatment such as ^{90}Y and

$^{177}$Lu.[9,10]$^{177}$Lu-octreotate/octreotide (DOTATATE/DOTATOC) PRRT, generated from ytterbium (Yb), is capable of delivering precise low dosages of β energies between 0.149 and 0.479 MeV with ranges of tissue penetration between 0.5 to 2.0 mm, and this property endows $^{177}$Lu-octreotate/octreotide with limited collateral damage to the normal tissues compared with $^{90}$Y. In addition, $^{177}$Lu has 2 main γ-emission energies, 0.113 MeV (relative abundance 6%) and 0.208 MeV (11%), thereby being provided as the adequate radiotracer for scintigraphic imaging during and after therapy, biodistribution, and dosimetry studies.[11] In 2015, Kim et al reviewed the efficacy of $^{177}$Lu-octreotate/octreotide PRRT and found that this treatment was very effective in inoperable or metastatic NETs patients.[12] Nevertheless, only single center trials were enrolled in the review. By far, there have been more single center trials and several multicentre randomized trials such as NETTER-1 about $^{177}$Lu-octreotate/octreotide PRRT in NETs. In this article we addressed and analyzed the efficacy and benefit of $^{177}$Lu-labeled PRRT for advanced NETs in recent years.

## 2. Materials and methods

### 2.1. Statement

This meta-analysis was based entirely on previous published studies which had declared ethical approvals and no original clinical raw data was collected or utilized, thereby ethical approval was not conducted for this study. This review was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA),[13] and the PRISMA checklist is shown in Table 1.

### 2.2. Search and selection strategy

An independent review of the PubMed, Cochrane Library, Web of Science, and Embase data bases was performed from Jan 1, 1950, to Apr 30, 2019. The search was implemented by using the following keywords

"Neuroendocrine Tumors" and "$^{177}$Lu-DOTATATE/DOTA-TOC". The complete search phrases used for PubMed were: ("DOTA" AND ("177Lu" OR "Lu177" OR "Lu-177" OR "177-Lu") AND ("neuroendocrine tumors"[MeSH Terms] OR "Neuroendocrine neoplasm"[Text Word] OR "Neuroendocrine Tumor"[Text Word] OR "Neuroendocrine carcinoma"[Text Word]). The searched articles were screened by Lin Lin and Meng-jiao Wang independently. Full texts were retrieved if they were confirmed to the eligibility criteria. If there were duplicates (patients' data from the same trial or institution), only the most complete, recent and relevant study was selected.

### 2.3. Inclusion and exclusion criteria

Inclusion criteria were as follows: randomised clinical trials (patients >10) with the utilityof $^{177}$Lu-DOTATATE/DOTATOC

**Table 1**

**PRISMA checklist.**

**PRISMA 2009 Checklist**

| Section/Topic | # | Checklist Item | Reported on Page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 2、3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3、4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 3、4 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | NA |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 4 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I$^2$) for each meta-analysis. | 4 |

**PRISMA 2009 Checklist**

| Section/Topic | # | Checklist Item | Reported on Page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 4 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 4 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 11 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | NA |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 4、5、12-14 |
| Synthesis of results | 21 | Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency. | 4、5、12-14 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | NA |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 4-5 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 5-6 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 5 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 6 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 6 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

PRISMA = preferred reporting items for systematic reviews and meta-analysis.

($^{177}$Lu-octreotate/octreotide) PRRT in adults with NETs. Exclusion criteria: randomised clinical trials (patients < 10), case reports, review articles, meetings, news, conferences, abstracts and editorials.

### 2.4. Data extraction and primary outcomes

The data were extracted by 2 reviewers (Lin Lin and Meng-jiao Wang), independently. The following information was collected from each trial: first author, number of patients, treatment compound, dosages of radiopharmaceuticals, treatment cycles, radiopharmaceuticals' cumulative activities and response criteria. The primary outcomes were disease response rates (DRRs) and disease control rates (DCRs). The definitions of DRRs and DCRs were described previously (DRRs = proportions of patients with complete response (CR) + partial response (PR), DCRs = proportions of patients with CR+ PR+ stable disease (SD)).[12] Overall survival (OS) and progression free survival (PFS) were not assessed because most of the trials were single-arm trials.

### 2.5. Statistical analysis

We used the Review Manager (version 5.3) for statistical analyses. The efficacy of $^{177}$Lu-octreotate/octreotide treatment was assessed depending on 2 indicators: DRRs and DCRs. A Cochran $Q$ test was used to assess heterogeneity between studies and $I^2$ statistic was used to show the magnitude of the heterogeneity. For categorical variables, the pooled estimation of effects was calculated with a random-effects model or a fixed-effects model. If $I^2$ value >50%, a random-effects model was used, otherwise we use a fixed-effects model. Funnel plots were performed to assess the potential publication bias. A 2-tailed $P$ value of less than .05 was considered statistically significant.

## 3. Results

### 3.1. Study characteristics

We identified a total of 716 articles, and thereof 148 conference reports/editorials/meetings/news and 445 reviews/case reports (patients < 10)/comments/abstracts were excluded. The remaining 123 potentially relevant publications were retrieved for detailed assessment,and 64 studies were excluded because the research subjects were irrelevant. After a further detailed review of the remained 59 articles, 37 articles were excluded for inadequate data or duplicated data, and 22 studies including 1758 patients were eligible for inclusion criteria. The flow chart is shown in Figure 1. For each selected study, data quantification was completely assessed.
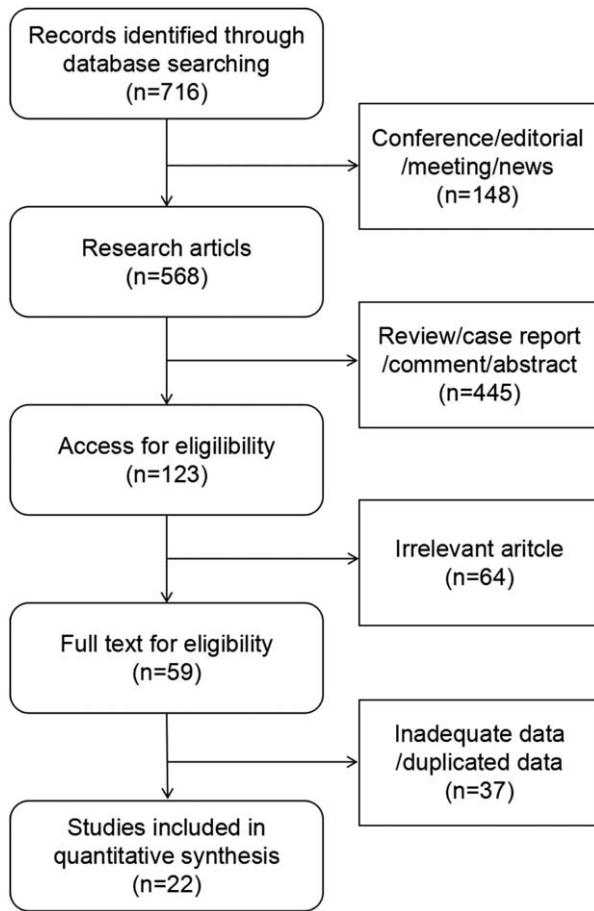
**Figure 1.** Selection of studies included in the meta-analysis.

In this meta-analysis, tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), RECIST 1.1, Southwest Oncology Group (SWOG) criteria, World Health Organization (WHO) criteria, or more than one criterion. 8 studies were evaluated by RECIST. 10 trials were evaluated by RECIST 1.1. Five trials were based on SWOG criteria. One trial was assessed by WHO criteria. There were 2 articles evaluated by 2 criteria, of them 1 by RECIST and RECIST 1.1, the other by RECIST 1.1 and SWOG.[14] The characteristics of these trials are shown in Table 2.

### 3.2. DRRs and DCRs

Detailed data of these selected studies data, DRRs and DCRs are demonstrated in Table 3. The pooled rates were presented with a random-effects model or a fixed-effects model on the basis of magnitude of the heterogeneity. There was only 1 article evaluated by WHO criteria, so it was not included in the following assessment.

***3.2.1. RECIST criteria group.*** For RECIST criteria, 8 studies with 478 patients were analyzed.[15–22] As shown in Figure 2, the test for heterogeneity showed heterogeneity for DRRs ($I^2 = 65\%$, $P = .006$). DRRs ranged between 16.7% and 53.0%. The random-effects model showed a pooled effect of 33.0% (95% CI: 25.0%-42.0%) for DRRs. As for DCRs, the test for heterogeneity performed no statistical significance ($I^2 = 0\%$, $P = .62$). DCRs ranged from 72.0% to 100%. The pooled effect was 79.0% (95% CI: 75.0%-83.0%) for DCRs according to the fixed-effects model.

***3.2.2. RECIST 1.1 criteria group.*** For RECIST1.1 criteria, 10 studies with 1127 patients were analyzed.[19,23–31] As shown in Figure 3, the test for heterogeneity showed heterogeneity for DRRs ($I^2 = 91\%$, $P < .001$). DRRs ranged between 10.0% and

### Table 2

**List of study characteristics.**

| First author | No. of total patients | Treatment compound | Dose (GBq) | 177 Lu cycles | Cumulative activity (GBq) | Median follow-up, mo | Response criteria |
|---|---|---|---|---|---|---|---|
| Garkavij 2010 (17) | 12 | DOTATATE | 7.4 | 3–4 | 26 (17–45) | 4–24 | RECIST |
| Swärd 2010 (21) | 16 | DOTATATE | 8 | 3 (1–5) | – | 5 | RECIST |
| Romer 2014 (20) | 16 | DOTATOC | 7.4 | 1–5 | 13.5±6.5 | 9 (1.0–80.1) | RECIST |
| Hamiditabar 2017 (18) | 28 | DOTATATE | 7.4 | 4 | 29.6 | 12.3 (2.5–49) | RECIST |
| Delpassand 2014 (16) | 32 | DOTATATE | 7.4 | 2–4 | 29.6 | 16.11 (0.3–26.8) | RECIST |
| Bodei 2011 (15) | 51 | DOTATATE | 3.7–7.4 | 4–6 | 25.2–29.2 | 60 | RECIST |
| Løitegård 2019 (19) | 79 | DOTATATE | – | 4 (1–10) | – | 45 (6–99) | RECIST/RECIST 1.1 |
| van Vliet 2013 (22) | 257 | DOTATATE | 3.7/7.4 | 4 | 22.2–29.6 | – | RECIST/SWOG |
| Limouris 2016 (28) | 13 | DOTATATE | 6.8 | 3–6 | 58 (13–77) | 4-24 | RECIST 1.1 |
| Parghane 2017 (29) | 19 | DOTATATE | 5.55 | 1–5 | – | – | RECIST 1.1 |
| Zandee WT 2019 (31) | 34 | DOTATATE | 7.4 | 4 | 7.4–29.6 | 18.1 (3.3–35.7) | RECIST 1.1 |
| Kalshetty 2018 (27) | 46 | DOTATATE | 5.55 | 4–5 | – | 1.5–4 | RECIST 1.1 |
| Demirci 2018 (25) | 160 | DOTATATE | 3.7–8.1 | 3–12 | – | 30.6 | RECIST 1.1 |
| Baum 2016 (23) | 32 | DOTATOC | 3.5–10.0 | 2–4 | 3.5–29.2 | 16.1±12.4 | RECIST 1.1 |
| Strosberg 2017 (30) | 101 | DOTATATE | 7.4 | 4 | 29.6 | 14 | RECIST1.1 |
| Garske-Román 2018 (26) | 200 | DOTATATE | 7.4 | 1–10 | 29.6 (5–74) | 31 (1–68) | RECIST1.1 |
| Brabander 2017 (24) | 443 | DOTATATE | 7.4 | 4 | 27.8–29.6 | 63 (55–72) | RECIST1.1 |
| Ianniello 2015 (33) | 15 | DOTATATE | 3.7 | 4–5 | 21.5 (12.9–27.8) | 29 (7–69) | SWOG |
| Paganelli 2014 (34) | 43 | DOTATATE | 3.7/5.5 | 5 | 18.45/27.8 | 25 (7–50) | SWOG |
| Sansovini 2017 (35) | 60 | DOTATATE | 3.7/5.5 | 5 | 18.5/27.8 | 59 (6.5–97) | SWOG |
| Ezziddin 2014 (32) | 74 | DOTATATE | 7.9 | 4 | – | 47 (44.5–49.5) | SWOG |
| Danthala 2014 (14) | 40 | DOTATATE | 7.4 | 1–6 | 7.4–44.4 | 6.2–50.2 | WHO |

RECIST = response evaluation criteria in solid tumors, SWOG = southwest oncology group, WHO = World Health Organization.

## Table 3

**Disease response and control rates of ^{177}Lu-labelled PRRT.**

| Criteria | Effects | No. of studies | Model | Pooled proportion (95% CI) | $I^2$(%) |
|---|---|---|---|---|---|
| RECIST | Response rates | 8 | Random-effects model | 0.33 (0.25–0.42) | 65 |
| | Control rates | 8 | Fixed-effects model | 0.79 (0.75–0.83) | 0 |
| RECIST 1.1 | Response rates | 10 | Random-effects model | 0.35 (0.26–0.45) | 91 |
| | Control rates | 10 | Random-effects model | 0.83 (0.78–0.88) | 77 |
| SWOG | Response rates | 5 | Random-effects model | 0.25 (0.16–0.36) | 84 |
| | Control rates | 5 | Random-effects model | 0.82 (0.75–0.89) | 66 |

CI = confidence interval, PRRT = peptide receptor radionuclide therapy, RECIST= response evaluation criteria in solid tumors, SWOG = southwest oncology group, WHO = World Health Organization.
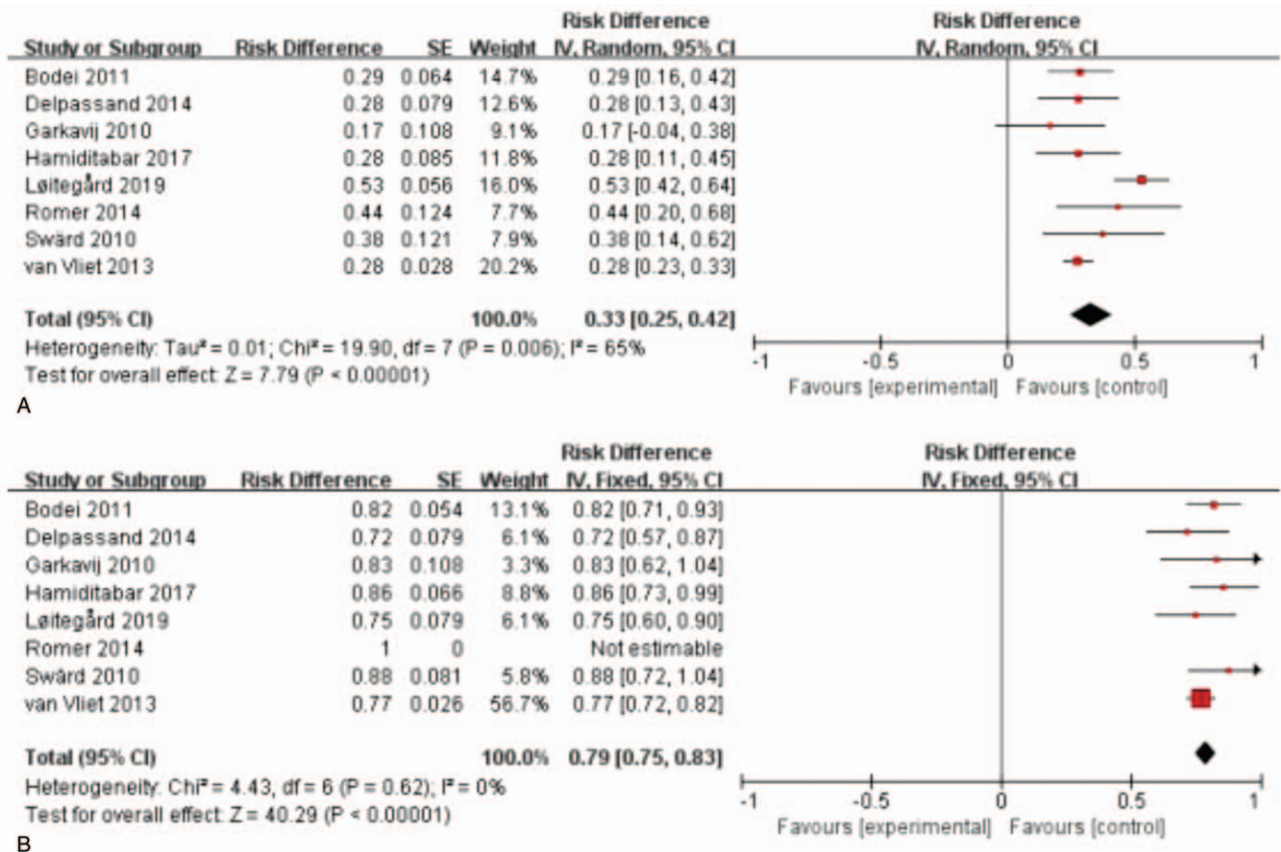
69.0%. The random-effects model showed a pooled effect of 35.0% (95% CI: 26.0%-45.0%) for DRRs. As for DCRs, the test for heterogeneity presented statistical significance ($I^2 = 77\%$, $P < .001$) among these articles. DCRs ranged from 68.0% to 93.8%. The pooled effect was 83.0% (95% CI: 78.0%-88.0%) for DCRs according to the random-effects model.

**3.2.3. SWOG criteria group.** For SWOG criteria, 5 studies with 459 patients were analyzed.[22,32–35] As shown in Figure 4, the test for heterogeneity showed heterogeneity for DRRs ($I^2 = 84\%$, $P < .001$). DRRs ranged between 7% and 36.5%. The random-effects model showed a pooled effect of 25.0% (95% CI: 14.0%-36.0%) for DRRs. For DCRs, the test for heterogeneity showed some significance ($I^2 = 66\%$, $P = .02$) among these articles. DCRs ranged from 74.0% to 89.2%. The pooled effect was 82.0%

(95% CI: 75.0%-89.0%) for DCRs according to the random-effects model.

## 4. Discussion

In this meta-analysis, 22 high-quality published articles containing 1758 inoperable or metastatic NETs patients who adopted ^{177}Lu-labelled PRRT were included. The evaluation of treatment efficacy was performed by RECIST or RECIST 1.1 or SWOG. The results showed that the pooled effects of DRRs were 33.0% (95% CI: 25.0%-42.0%) by RECIST, 35.0% (95% CI: 26.0%-45.0%) by RECIST 1.1 and 25.0% (95% CI: 14.0%-36.0%) by SWOG, while the DCRs were 79.0% (95% CI: 75.0%-83.0%) by RECIST, 83.0% (95% CI: 78.0%-88.0%) by RECIST 1.1 and 82.0% (95% CI: 75.0%-89.0%) by SWOG. Based on these



**Figure 2.** Forest plots of proportions of disease response rates (A) and disease control rates (B) in RECIST criteria group. RECIST= response evaluation criteria in solid tumors.

| Study or Subgroup | Risk Difference | SE | Weight | Risk Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Baum 2016 | 0.41 | 0.087 | 8.7% | 0.41 [0.24, 0.58] |
| Brabander 2017 | 0.39 | 0.023 | 11.8% | 0.39 [0.34, 0.44] |
| Demirci 2018 | 0.5 | 0.04 | 11.2% | 0.50 [0.42, 0.58] |
| Garske-Román 2018 | 0.24 | 0.03 | 11.6% | 0.24 [0.18, 0.30] |
| Kalshetty 2018 | 0.43 | 0.073 | 9.5% | 0.43 [0.29, 0.57] |
| Limouris 2016 | 0.69 | 0.128 | 6.5% | 0.69 [0.44, 0.94] |
| Loitegård 2019 | 0.17 | 0.042 | 11.1% | 0.17 [0.09, 0.25] |
| Parghane 2017 | 0.1 | 0.069 | 9.7% | 0.10 [-0.04, 0.24] |
| Strosberg 2017 | 0.18 | 0.038 | 11.3% | 0.18 [0.11, 0.25] |
| Zandee WT 2019 | 0.59 | 0.084 | 8.8% | 0.59 [0.43, 0.75] |
| **Total (95% CI)** | | | **100.0%** | **0.35 [0.26, 0.45]** |

Heterogeneity: Tau² = 0.02; Chi² = 95.07, df = 9 (P < 0.00001); I² = 91%
Test for overall effect: Z = 7.33 (P < 0.00001)

A

| Study or Subgroup | Risk Difference | SE | Weight | Risk Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Baum 2016 | 0.94 | 0.043 | 10.7% | 0.94 [0.86, 1.02] |
| Brabander 2017 | 0.82 | 0.018 | 14.2% | 0.82 [0.78, 0.86] |
| Demirci 2018 | 0.72 | 0.036 | 11.8% | 0.72 [0.65, 0.79] |
| Garske-Román 2018 | 0.92 | 0.02 | 14.0% | 0.92 [0.88, 0.96] |
| Kalshetty 2018 | 0.79 | 0.06 | 8.4% | 0.79 [0.67, 0.91] |
| Limouris 2016 | 0.92 | 0.075 | 6.7% | 0.92 [0.77, 1.07] |
| Loitegård 2019 | 0.85 | 0.04 | 11.2% | 0.85 [0.77, 0.93] |
| Parghane 2017 | 0.68 | 0.107 | 4.2% | 0.68 [0.47, 0.89] |
| Strosberg 2017 | 0.79 | 0.04 | 11.2% | 0.79 [0.71, 0.87] |
| Zandee WT 2019 | 0.82 | 0.065 | 7.7% | 0.82 [0.69, 0.95] |
| **Total (95% CI)** | | | **100.0%** | **0.83 [0.78, 0.88]** |

Heterogeneity: Tau² = 0.00; Chi² = 39.19, df = 9 (P < 0.0001); I² = 77%
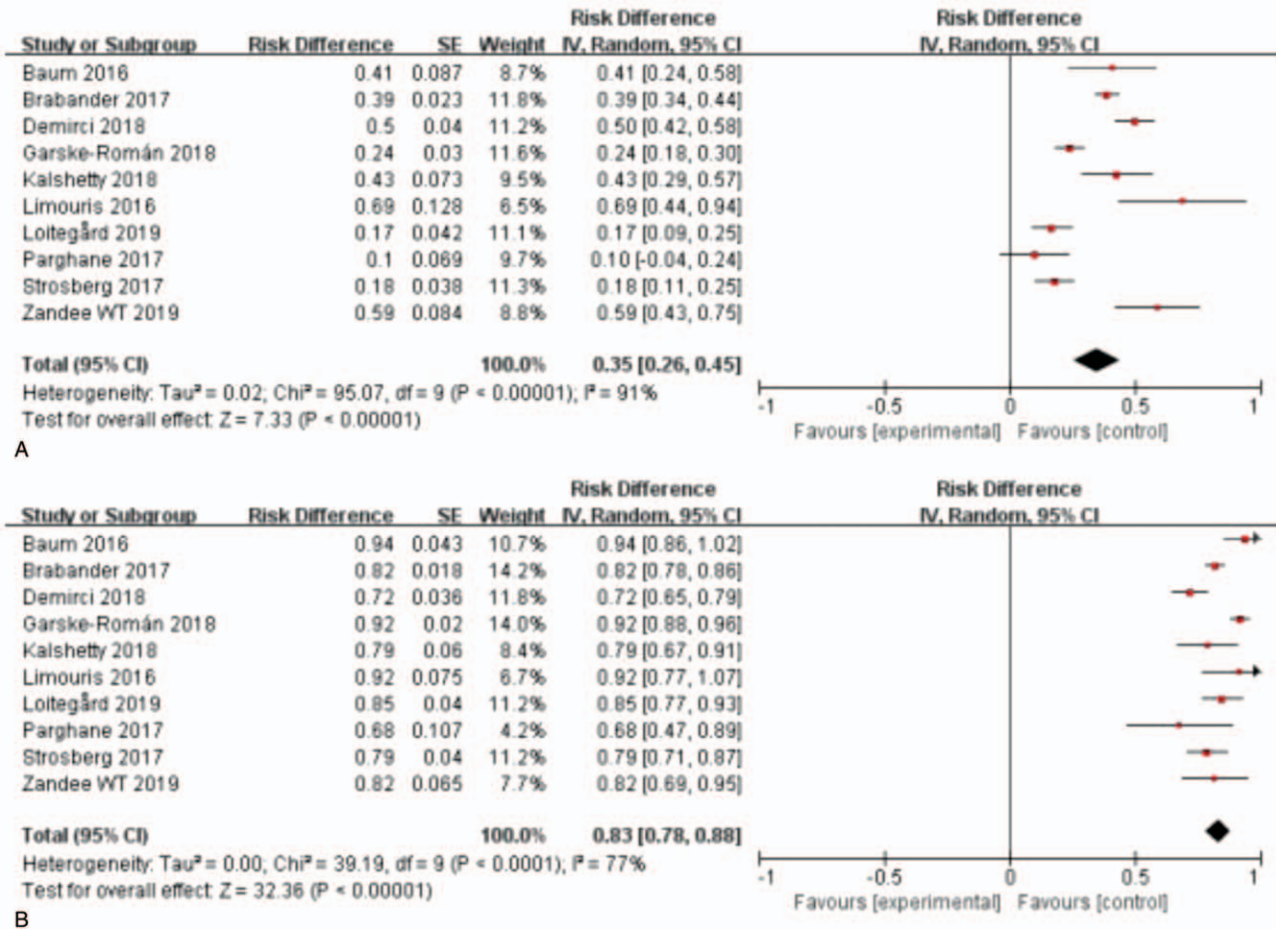Test for overall effect: Z = 32.36 (P < 0.00001)

B

**Figure 3.** Forest plots of proportions of disease response rates (A) and disease control rates (B) in RECIST 1.1 criteria group. RECIST= response evaluation criteria in solid tumors.
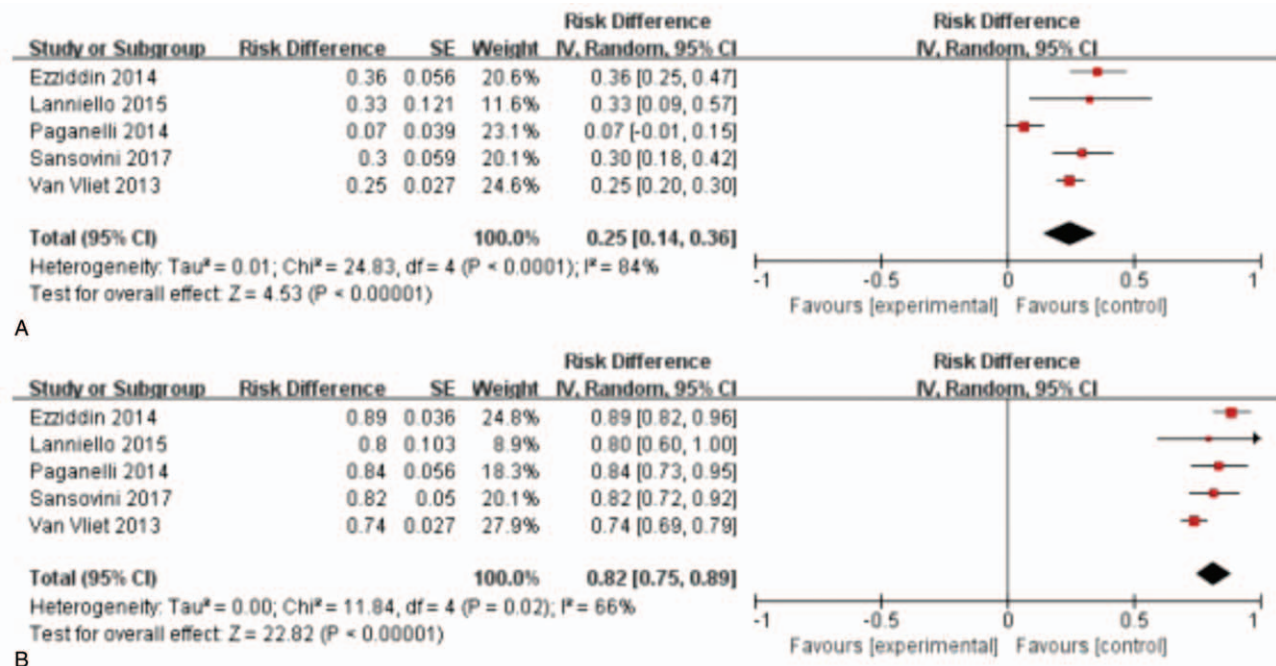
| Study or Subgroup | Risk Difference | SE | Weight | Risk Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Ezziddin 2014 | 0.36 | 0.056 | 20.6% | 0.36 [0.25, 0.47] |
| Lanniello 2015 | 0.33 | 0.121 | 11.6% | 0.33 [0.09, 0.57] |
| Paganelli 2014 | 0.07 | 0.039 | 23.1% | 0.07 [-0.01, 0.15] |
| Sansovini 2017 | 0.3 | 0.059 | 20.1% | 0.30 [0.18, 0.42] |
| Van Vliet 2013 | 0.25 | 0.027 | 24.6% | 0.25 [0.20, 0.30] |
| **Total (95% CI)** | | | **100.0%** | **0.25 [0.14, 0.36]** |

Heterogeneity: Tau² = 0.01; Chi² = 24.83, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 4.53 (P < 0.00001)

A

| Study or Subgroup | Risk Difference | SE | Weight | Risk Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Ezziddin 2014 | 0.89 | 0.036 | 24.8% | 0.89 [0.82, 0.96] |
| Lanniello 2015 | 0.8 | 0.103 | 8.9% | 0.80 [0.60, 1.00] |
| Paganelli 2014 | 0.84 | 0.056 | 18.3% | 0.84 [0.73, 0.95] |
| Sansovini 2017 | 0.82 | 0.05 | 20.1% | 0.82 [0.72, 0.92] |
| Van Vliet 2013 | 0.74 | 0.027 | 27.9% | 0.74 [0.69, 0.79] |
| **Total (95% CI)** | | | **100.0%** | **0.82 [0.75, 0.89]** |

Heterogeneity: Tau² = 0.00; Chi² = 11.84, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 22.82 (P < 0.00001)

B

**Figure 4.** Forest plots of proportions of disease response rates (A) and disease control rates (B) in SWOG criteria group. SWOG = southwest oncology group.

results, we concluded that ^{177}Lu-labelled PRRT displayed encouraging treatment efficiency for advanced NETs.

Meanwhile, $I^2$ statistical test demonstrated significant heterogeneity among the studies in different criteria groups with an exception of the analysis of DCRs in RECIST criteria group. The heterogeneity may be attributed to differences in basic characteristics of the study populations, locations of the study, drug compliance in each study, batch of drug and correction of relevant factors. Due to the limited information in individual studies, subgroup analysis or meta-regression were not applicable to assay the sources of heterogeneity in this meta-analysis. In consequence, the results of this analysis should be interpreted with caution especially when extrapolation was considered.

Recently, a phase III clinical trial (NETTER-1) designed for evaluating the efficacy and safety of ^{177}Lu-DOTATATE PRRT in patients with advanced, SSTR positive and G1/G2 midgut NET has published their stage results.[30] At the data cutoff date for the cohort, compared to the control group (high-dose octreotide long-acting repeatable group), ^{177}Lu-DOTATATE group had more patients survived more than 20 months (65.2% vs 10.8%). The DRR, evaluated by RECIST 1.1, was 18% in the ^{177}Lu-DOTATATE group while in the control group it was 3% ($P < .001$). Another large clinical trial with over 200 patients treated with ^{177}Lu-DOTATATEPRRT showed that the quality of life and symptoms were improved in 40% to 70% of cases depending on the preexistence of a certain condition.[36] Strosberg et al found that compared with the control group (high-dose octreotide long-acting repeatable group), ^{177}Lu-DOTATATE PRRT group demonstrated a longer PFS (28.4 months vs 8.5 months).[37] Altogether, repeated cycles of ^{177}Lu-DOTATATE PRRT provided an obvious improvement of the quality of life and prolonged the patients' survival time.

There was no obvious acute toxicity during or immediately after the ^{177}Lu-DOTATATE treatment. The maximum toleration of this treatment was up to 29 GBq cumulative activity (up to 7.4 GBq/cycle) with minimal hematological or renal damage.[15,25] In a study by Danthala et al, there was no significant impact on white blood cells or platelets and no renal toxicity was observed during PRRT with ^{177}Lu-DOTATOC and 24 months after treatment.[14] Nausea and vomiting were the most common side effects, followed by transient skin redness.[16] Delpassand et al. found that hematological toxicity and bone metastasis may occur after the repeated cycles of ^{177}Lu-DOTATATE PRRT, and these side effects were associated with the prior history of chemotherapy treatment.[16]

## 5. Conclusion

This meta-analysis demonstrated that the curative effect of repeated treatment with ^{177}Lu-octreotate/octreotide PRRT was promising in advanced NETs patients. Up to date, there are still several clinical studies in progression, so we will get more information to validate this therapeutic modality.

## Author contributions

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## References

[1] Oronsky B, Ma PC, Morgensztern D, et al. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia 2017;19:991–1002.

[2] Guadagno E, De Caro Mdel B, Insabato L. An update on the pathology of neuroendocrine tumors. Front Biosci 2016;8:1–2.

[3] Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335–42.

[4] Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.

[5] Chauhan A, Yu Q, Ray N, et al. Global burden of neuroendocrine tumors and changing incidence in Kentucky. Oncotarget 2018;9: 19245–54.

[6] Taal BG, Visser OJN. Epidemiology of neuroendocrine tumours. Neuroendocrinology 2004;80:3–7.

[7] Narayanan S, Kunz PL. Role of somatostatin analogues in the treatment of neuroendocrine tumors. Hematol Oncol Clin North Am 2016;30: 163–77.

[8] Krenning EP, Kooij PP, Bakker WH, et al. Radiotherapy with a radiolabeled somatostatin analogue, [111In-DTPA-D-Phe1]-octreotide. A case history. Ann N Y Acad Sci 2010;733:496–506.

[9] Zlatko D, Jarrett R, Braat AJA, et al. The efficacy of hepatic ^{90}Y resin radioembolization for metastatic neuroendocrine tumors: a meta-analysis. J Nucl Med 2014;55:1404–10.

[10] Seregni E, Maccauro M, Coliva A, et al. Treatment with tandem [^{90}Y] DOTA-TATE and [^{177}Lu] DOTA-TATE of neuroendocrine tumors refractory to conventional therapy: preliminary results. Q J Nucl Med Mol Imaging 2010;54:84–91.

[11] Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40:800–16.

[12] Kim SJ, Pak K, Koo PJ, et al. The efficacy of 177Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis. Eur J Nucl Med Mol Imaging 2015;42:1964–70.

[13] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.

[14] Danthala M, Kallur KG, Prashant GR, et al. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours: 5 years' experience from a tertiary cancer care centre in India. Eur J Nucl Med Mol Imaging 2014;41:1319–26.

[15] Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with 177 Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging 2011;38:2125–35.

[16] Delpassand ES, Samarghandi A, Zamanian S, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE for patients with somatostatin receptor-expressing neuroendocrine tumors: the first US phase 2 experience. Pancreas 2014;43:518–25.

[17] Michael G, Mattias N, Katarina SGG, et al. 177Lu-[DOTA0,Tyr3] octreotate therapy in patients with disseminated neuroendocrine tumors: analysis of dosimetry with impact on future therapeutic strategy. Cancer 2010;116(S4):1084–92.

[18] Hamiditabar M, Ali M, Roys J, et al. Peptide receptor radionuclide therapy with 177Lu-Octreotate in patients with somatostatin receptor expressing neuroendocrine tumors: six years' assessment. Clin Nucl Med 2017;42:436–43.

[19] Loitegard T, Berntzen DT, Thiis-Evensen E. The RECIST criteria compared to conventional response evaluation after peptide receptor radionuclide therapy in patients with neuroendocrine neoplasms. Ann Nucl Med 2019;33:147–52.

[20] Romer A, Seiler D, Marincek N, et al. Somatostatin-based radiopeptide therapy with [177Lu-DOTA]-TOC versus [90Y-DOTA]-TOC in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2014;41: 214–22.

[21] Sward C, Bernhardt P, Ahlman H, et al. [177Lu-DOTA 0-Tyr 3]-octreotate treatment in patients with disseminated gastroenteropancreatic neuroendocrine tumors: the value of measuring absorbed dose to the kidney. World J Surg 2010;34:1368–72.

[22] Vliet EI, Van , Krenning EP, et al. Comparison of response evaluation in patients with gastroenteropancreatic and thoracic neuroendocrine tumors after treatment with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med 2013;54:1689–96.

[23] Baum RP, Kluge AW, Harshad K, et al. [177Lu-DOTA]0-D-Phe1-Tyr3-Octreotide (177Lu-DOTATOC) for peptide receptor radiotherapy in patients with advanced neuroendocrine tumours: a phase-II study. Theranostics 2016;6:501–10.

[24] Brabander T, Wa VDZ, Teunissen JJ, et al. Long-term efficacy, survival and safety of [177Lu-DOTA0,Tyr3]octreotate in patients with gastro-enteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res 2017;23:4617–24.

[25] Demirci E, Kabasakal L, Toklu T, et al. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours including high-grade (WHO G3) neuroendocrine tumours: response to treatment and long-term survival update. Nucl Med Commun 2018;39:789.

[26] Garskeromán U, Sandström M, Fröss KB, et al. Prospective observational study of 177Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. Eur J Nucl Med Mol Imaging 2018;45:970–88.

[27] Kalshetty A, Ramaswamy A, Ostwal V, et al. Resistant functioning and/or progressive symptomatic metastatic gastroenteropancreatic neuroendocrine tumors: efficacy of 177Lu-DOTATATE peptide receptor radionuclide therapy in this setting. Nucl Med Commun 2018;39:39.

[28] Limouris GS, Poulantzas V, Trompoukis N, et al. Comparison of 111In-[DTPA0]Octreotide versus non carrier added 177Lu- [DOTA0,Tyr3]-octreotate efficacy in patients with GEP-NET treated intra-arterially for liver metastases. Clin Nucl Med 2016;41:194.

[29] Parghane RV, Talole S, Prabhash K, et al. Clinical response profile of metastatic/advanced pulmonary neuroendocrine tumors to peptide receptor radionuclide therapy with 177Lu-DOTATATE. Clin Nucl Med 2017;42:428–35.

[30] Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017; 376:125–35.

[31] Zandee WT, Brabander T, Blazevic A, et al. Symptomatic and radiological response to 177Lu-DOTATATE for the treatment of functioning pancreatic neuroendocrine tumors. J Clin Endocrinol Metab 2019;104:1336–44.

[32] Ezziddin S, Khalaf F, Vanezi M, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2014;41:925–33.

[33] Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and 18F-FDG PET. Eur J Nucl Med Mol Imaging 2015;43:1040–6.

[34] Paganelli G, Sansovini M, Ambrosetti A, et al. 177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study. Eur J Nucl Med Mol Imaging 2014;41:1845–51.

[35] Sansovini M, Severi S, Ianniello A, et al. Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with 177Lu-D OTATATE. Eur J Nucl Med Mol Imaging 2016;44:1–0.

[36] Khan S, Krenning EP, Essen MV, et al. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]Octreotate. J Nucl Med 2011;52:1361.

[37] Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with 177Lu-Dotatate in the Phase III NETTER-1 trial. J Clin Oncol 2018;36:2578–84.