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ORIGINAL ARTICLE

The efficacy of ^{177}Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis

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Abstract
Purpose This study was performed to evaluate the efficacy of ^{177}Lu-labelled peptide receptor radionuclide therapy (PRRT) in patients with inoperable or metastatic neuroendocrine tumours (NETs).
Methods Systematic searches of MEDLINE and EMBASE databases were performed using the keywords of "neuroendocrine", "^{177}Lu" and "prognosis". All published studies of neuroendocrine tumours treated with ^{177}Lu-labelled radiopharmaceuticals and evaluated with either Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 or Southwest Oncology Group (SWOG) criteria or both were included. If there was more than one published study from the same institution, only one report with the information most relevant to this study was included. Each response criteria group was analysed for disease response rates and disease control rates, defined as the percentages of patients with complete response (CR)+partial response (PR), and CR+PR+stable disease (SD), respectively, to a therapeutic intervention in clinical trials of anticancer agents. The pooled proportions are presented with both a fixed-effects model and random-effects model.
Results Six studies with 473 patients (4 in RECIST criteria group with 356 patients, 3 in SWOG criteria group with 375 patients and 1 in both groups) were included. The RECIST criteria group demonstrated disease response rates ranging between 17.6 and 43.8 % with a pooled effect of 29 % [95 % confidence interval (CI) 24–34 %]. Disease control rates ranged from 71.8 to 100 %. The random-effects model showed an average disease control rate of 81 % (95 % CI 71–91 %). The SWOG criteria group demonstrated disease response rates ranging between 7.0 and 36.5 % with a pooled effect of 23 % (95 % CI 11–38 %). Disease control rates ranged from 73.9 to 89.1 %. The random-effects model showed an average disease control rate of 82 % (95 % CI 71–91 %).
Conclusion ^{177}Lu-labelled PRRT is an effective treatment option for patients with inoperable or metastatic NETs.

Keywords Neuroendocrine tumour · Lutetium · Radionuclide therapy · Peptide receptor therapy

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Introduction

The annual incidence of neuroendocrine tumours (NETs) has been rising over the past 30 years from 1.09/100,000 to 5.25/100,000 according to the Surveillance, Epidemiology, and End Results (SEER) Program registries [1]. In addition, 40 % of the patients with NETs present with localized disease only, 17 % with regional disease and 20 % with distant metastases [1]. Surgery is the only potentially curative therapy; however, NETs are no longer resectable if metastatic disease is present [1]. For unresectable metastatic disease, treatment options include octreotide therapy, chemotherapy, interferon alpha, molecular targeted agents or interventional treatments for hepatic metastases [2].

In the mid 1990s, peptide receptor radionuclide therapy (PRRT) was investigated in patients with inoperable or metastatic NETs [3]. It was first introduced by European centres with encouraging results by replacing ^{111}In-labelled somatostatin peptide receptor radionuclides with ^{90}Y [4] and ^{177}Lu peptide [5]-labelled somatostatin peptide receptor radionuclides. ^{90}Y is a high-energy beta emitter with maximal tissue penetration of 12 mm. ^{177}Lu is a medium-energy beta emitter with maximal tissue penetration of 2 mm. Although there was no difference in overall survival (OS) between patient groups undergoing PRRT with ^{90}Y and ^{177}Lu [6], the advantage of using ^{90}Y for larger tumours and ^{177}Lu for smaller tumours was suggested, based on animal models [7]. PRRT is generally well tolerated with a major concern for nephrotoxicity and haematotoxicity [8]. However, the risk of nephrotoxicity or haematotoxicity is less with ^{177}Lu-labelled PRRT [9]. In addition, ^{177}Lu-labelled PRRT was recently approved for clinical trials by the US Food and Drug Administration (FDA). The aim of this study was to evaluate the efficacy of ^{177}Lu-labelled PRRT in patients with inoperable or metastatic NETs.

Materials and methods

Data search and study selection

We performed systematic searches of MEDLINE (from inception to September 2014) and EMBASE (from inception to September 2014) databases for English-language publications using the keywords of "neuroendocrine", "^{177}Lu" and "prognosis". All searches were limited to human studies. All published studies of neuroendocrine tumours treated with ^{177}Lu-labelled radiopharmaceuticals and evaluated with Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 or 1.1, Southwest Oncology Group (SWOG) criteria or World Health Organization (WHO) criteria were searched. Review articles, abstracts and editorials were excluded, and duplicate data were removed. If there was more than one published study from the same institution, only one report with the information most relevant to this study was included. Two authors performed the searches and screening independently, and reviewed according to the Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analyses. Discrepancies were resolved by consensus [10].

Data extraction and statistical analysis

Data were extracted from the publications independently by two reviewers, and the following information was recorded: first author, year of publication, country, study design, dose of radiopharmaceuticals, number of patients and response criteria. The studies were grouped according to the response criteria used for evaluation. Effect sizes were proportions of disease response rates and disease control rates (expressed as a percentage) with 95 % confidence interval (CI). Disease response rates and disease control rates were defined as the percentages of patients with complete response (CR)+partial response (PR), and CR+PR+stable disease (SD), respectively, to a therapeutic intervention in clinical trials of anticancer agents. The pooled proportions are presented with both a fixed-effects model and random-effects model. Heterogeneity among studies was assessed using Cochran's Q and I^2 statistics, as described previously [11]. The data from each study were analysed using MedCalc Statistical Software version 14.12.0 (MedCalc Software, Ostend, Belgium). The authors followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA); the PRISMA Statement and checklist are presented in Table 1 [12].

Results

Study characteristics

The electronic searches identified 133 articles. There were 56 conference abstracts and 42 studies that did not meet the inclusion criteria based on their title and abstract and were excluded. After reviewing the full text of the remaining 21 articles, 6 studies including 473 patients were eligible for inclusion in the study. Most studies were excluded due to duplicated data. The detailed procedure is shown in Fig. 1. Quality assessment was conducted on all six studies. Generally, studies met most of the quality criteria. In this meta-analysis, studies providing either RECIST 1.0 [6, 13, 14] or SWOG [15, 16] data or both [17] were included. Since there were only one study evaluated with RECIST 1.1 [18] and one study evaluated with WHO [19] criteria, respectively, and group analysis cannot be performed for these single studies, these criteria could not be included in this study. Data of two studies from Bodei et al. [13] and Paganelli et al. [15] might be duplicated; however, they were published from different institutions and the response criteria adopted in each study were different (Bodei et al., RECIST; Paganelli et al., SWOG). Three studies were prospective [13–15]. The others were designed retrospectively [6, 16, 17]. A total of 457 patients from 5 studies were treated with [^{177}Lu-DOTA^0,Tyr^3]octreotate (DOTATATE) [13–17], whereas the other 16 patients from 1 study were treated with [^{177}Lu-DOTA^0,Tyr^3]octreotide (DOTATOC) [6]. Patients received from one to five cycles of treatment with each dose of 3.7–7.4 GBq. Cumulative activity in patients included in this meta-analysis ranged between 3.7 and 29.6 GBq. No major toxicity was observed except one study by Romer et al., which reported haematotoxicity and severe permanent renal toxicity [6]. The study characteristics are summarized in Table 2.

Table 1 PRISMA Statement and checklist of the study

Section/topic	#	Checklist item	Yes (Y)/ no (N)
Title	1	Identify the report as a systematic review, meta-analysis or both	Y
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	Y
Rationale	3	Describe the rationale for the review in the context of what is already known	Y
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS)	Y
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	Y
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	Y
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	Y
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	N
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)	Y
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	Y
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	Y
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	N
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	Y
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	Y
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)	Y
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified	Y
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	Y
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	Y
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)	Y
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Y
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Y
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	N
Additional analysis	23	Give results of additional analyses, if done [e.g. sensitivity or subgroup analyses, meta-regression (see item 16)]	Y
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, health care providers, users and policymakers)	Y
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)	Y
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	Y
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	Y

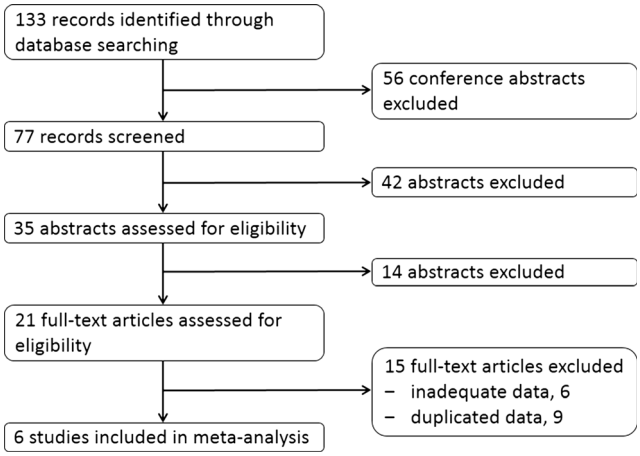

Fig. 1 Flowchart of the study selection process

Disease response and control rates

Disease response rates and disease control rates of included studies are presented in Table 3 according to the response criteria adopted in each study. The pooled rates are presented with both a fixed-effects model and random-effects model.

RECIST criteria group (Fig. 2)

Four studies with 356 patients were included in the group analysis of RECIST criteria [6, 13, 14, 17]. The test for heterogeneity demonstrated no observed heterogeneity for disease response rates (I^2=0 %). Disease response rates ranged between 17.6 and 43.8 % with a pooled effect of 29 % (95 % CI 24–34 %). Disease control rates ranged from 71.8 to 100 %. The random-effects model showed an average disease control rate of 81 % (95 % CI 71–91 %).

Table 3 Disease response and control rates of ^{177}Lu-labelled PRRT

Criteria	Effects	No. of studies	Models	Pooled proportion (95 % CI)	I^2 (%)
RECIST	Response rates	4	Fixed-effects Random-effects	0.29 (0.24–0.34) 0.29 (0.24–0.34)	0
	Control rates	4	Fixed-effects Random-effects	0.78 (0.73–0.82) 0.81 (0.71–0.91)	72.3
SWOG	Response rates	3	Fixed-effects Random-effects	0.25 (0.21–0.30) 0.23 (0.11–0.38)	86.5
	Control rates	3	Fixed-effects Random-effects	0.78 (0.74–0.82) 0.82 (0.71–0.91)	78.8

I^2 the percentage of total variation across studies due to heterogeneity rather than chance, I^2 =100 % x (Q − df)/Q, where Q is Cochran's heterogeneity statistics and df, the degree of freedom

SWOG criteria group (Fig. 3)

Three studies with 374 patients were included in the group analysis of SWOG criteria [15–17]. The test for heterogeneity showed a significant result for disease response rates (I^2= 86.5 %). Disease response rates ranged between 7.0 and 36.5 % with a pooled effect of 23 % (95 % CI 11–38 %). Disease control rates ranged from 73.9 to 89.1 %. The random-effects model showed an average disease control rate of 82 % (95 % CI 71–91 %).

Discussion

NETs have shown a fivefold increase over the last 30 years, greater than many other gastrointestinal malignancies, 20 % of which are diagnosed with distant disease at the time of presentation [1]. Although a number of different systems have

Table 2 Studies included in the current meta-analysis

First author	Year	Country	Compound	Dose (GBq)	^{177} Lu cycles	Cumulative Activity (GBq)	No. of patients	% of pancreatic NETs	Study design	Follow-up (months): median (range)	Response criteria
Bodei [13]	2011	Italy	DOTATATE	3.7~7.4	4~6	3.7~29.2	51	14	*P* (phase I–II)	60 (5~86)	RECIST
Romer [6]	2013	Switzerland	DOTATOC	–	1~5	13.5	16	–	–	9 (1~80.1)	RECIST
van Vliet [17]	2013	Netherlands	DOTATATE	3.7/7.4	4	22.2~29.6	257	27	*R*	–	RECIST/ SWOG
Delpassand [14]	2014	USA	DOTATATE	7.4	1~4	29.6	32	–	*P* (phase II)	0.3~26.8	RECIST
Paganelli [15]	2014	Italy	DOTATATE	3.7/5.5	5	14.4~27.8	43	0	*P* (phase II)	38 (11~59)	SWOG
Ezziddin [16]	2014	Germany	DOTATATE	7.9	4	-	74	45	*R*	47	SWOG

P prospective, *R* retrospective

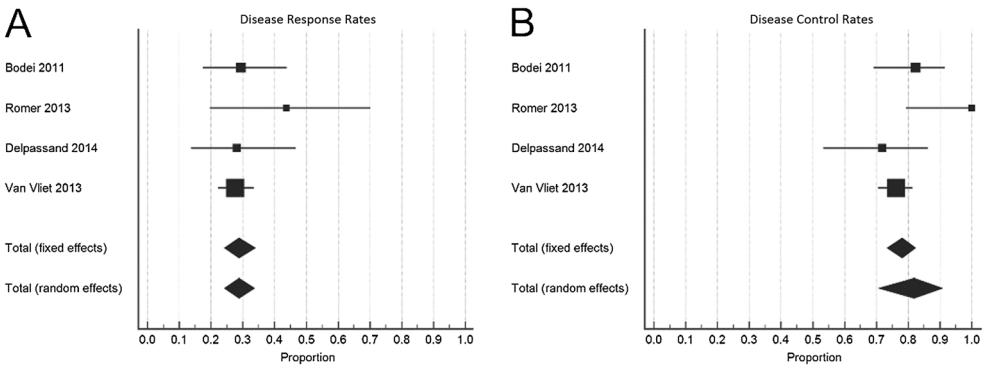

Fig. 2 Forest plots of proportions of disease response rates (**a**) and disease control rates (**b**) in RECIST 1.0 criteria group

been primarily developed to grade and classify NETs, these classifications are also useful in the prognostication and management of patients [20]. Low-/intermediate-grade or well-differentiated NETs are relatively indolent [20]. The clinical presentation of NETs depends on excessive secretion of hormones from the tumour cells [21]. NETs are classified as functional or non-functional tumours according to their associated clinical syndromes [22]. First-line therapy in NETs is somatostatin analogues in NETs with distant metastases according to European Neuroendocrine Tumor Society (ENETS) guidelines [21]. Second-line therapies include interferon alpha for functioning NETs and PRRT for both functioning and non-functioning NETs after the failure of somatostatin analogues [21]. However, PRRT has not been included in the management of NETs with unresectable or distant metastatic disease according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [23].

The indications for PRRT are relatively universal: unresectable NETs or distant metastatic disease [24]. High radiotracer uptake of tumour lesions on ^{111}In-octreotide scintigraphy or ^{68}Ga-somatostatin analogue positron emission tomography (PET) is a prerequisite for PRRT [21]. There are differences in protocols and octreotide analogues, which can have an effect on the efficacy of PRRT. In studies by Delpassand et al. [14] and Ezziddin et al. [16], patients were treated with a fixed dose of 7.4 or 7.9 GBq in each cycle. However, cycle doses varied between 3.7 and 7.4 GBq in other studies [13, 15, 17]. In a study by van Vliet et al. [17], the single dose was dependent on short-term toxicity, while cumulative activity was determined by the basis of the presence of risk factors for kidney and bone marrow toxicity in a study by Paganelli et al. [15]. This protocol standardization issue has been recently raised by Bodei et al. [25]. Standardization and a randomized controlled trial are critically necessary steps to determine the role of PRRT for the treatment of patients with NETs [25]. Hepatotoxicity and haematotoxicity may have limited the use of PRRT in some cases. Few adverse effects of PRRT were reported according to the study by Kwekkeboom et al. [26]. Acute haematological toxicity is usually mild and self-limiting [27]. Of 504 patients, 3 developed myelodysplastic syndrome [26]. The kidney is also a dose-limiting organ for PRRT [2]. Nephrotoxicity is a consequence of proximal tubular reabsorption of filtered radiopeptides with subsequent radiation to the glomeruli [28]. To protect kidneys from PRRT, amino acid solution is administered [27], though it can cause nausea and headache [2]. In most cases, PRRT was generally well tolerated. Compared to ^{90}Y-labelled PRRT, ^{177}Lu-labelled PRRT emits lower energy beta radiation and has a shorter emission range. Therefore, it demonstrates a more localized radiation effect and less radiation effects in the kidneys or bone marrow, leading to less adverse effects [29].

^{177}Lu-Labelled PRRT showed a survival benefit of 40–72 months from diagnosis, compared with historical controls in a study by Kwekkeboom et al. [26]. The current study has evaluated the efficacy of ^{177}Lu-labelled PRRT in patients with NETs. Although PRRT protocols were

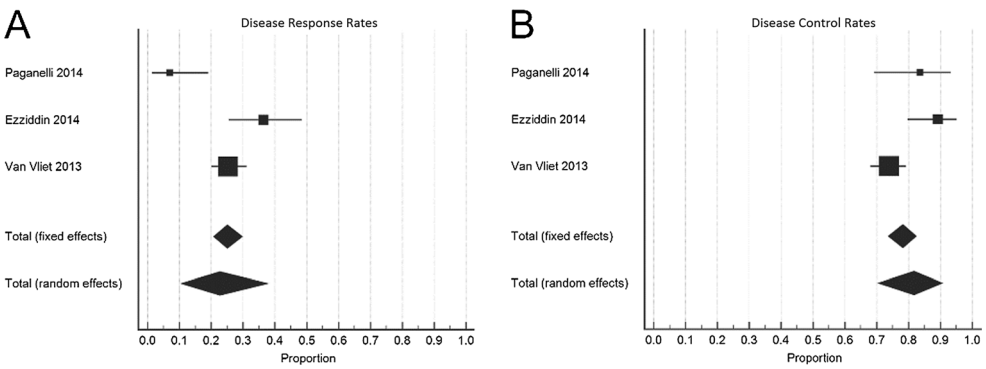

Fig. 3 Forest plots of proportions of disease response rates (**a**) and disease control rates (**b**) in SWOG criteria group

different among the centres and complete remission was extremely rare, the pooled efficacy results of PRRT including all protocols were satisfactory; disease response and disease control rates were 29 and 81 % using the RECIST 1.0 criteria, respectively, and 23 and 82 % using the SWOG criteria. In a clinical setting, when a patient is stabilized by the new treatment such as PRRT after progression, this is considered as a response.

The pooled effects of the SWOG criteria group are similar to those of the RECIST criteria group. However, there are several major differences between RECIST and SWOG criteria. RECIST 1.0 measures the longest diameters of up to five lesions per organ and ten lesions in total; SWOG calculates the sum of products of perpendicular diameters of up to three lesions per organ. They also have different definitions for response criteria of CR, PR, SD and progressive disease. Caution should be used for the interpretation of the results of the SWOG criteria group, for the group had very large inconsistency (I^2=78.8–86.5 %) in the included studies' results. The results of the current study are similar to those of a study published by Claringbold et al. using the RECIST 1.1 criteria [18]: disease response rate of 24 % and disease control rate of 94 %. Despite these similar good results from several studies, PRRT is often criticized as an investigational approach in large part due to the lack of any prospective randomized controlled trials. Nowadays, there is an ongoing multicentre randomized trial comparing ^{177}Lu-labelled PRRT with supportive care of octreotide (NETTER-1, NCT01578239).

Conclusion

In conclusion, although the treatment protocols are not standardized and the treatment effects should be further verified through prospective randomized controlled trials, ^{177}Lu-labelled PRRT is an effective treatment option for patients with inoperable or metastatic NETs, based on this meta-analysis of the published data.

Compliance with ethical standards

Funding This study was not funded by any organization.

Conflicts of interest None.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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