Radioligand Therapy in Patients with Lung Neuroendocrine Tumors: A Systematic Review on Efficacy and Safety

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Short Title: Radioligand Therapy in Lung NET

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Abstract

Introduction: Neuroendocrine neoplasms, arising from various sites, present therapeutic challenges. Radioligand therapy (RLT) has emerged as a promising approach for unresectable/metastatic NENs of midgut origin with increased somatostatin receptor (SSTR) uptake. The aim of this review is to assess the efficacy and safety of RLT in patients with lung neuroendocrine tumors (NETs). **Methods:** Following PRISMA guidelines, a systematic review of MEDLINE and EMBASE databases retrieved English articles until March 31, 2023. Inclusion criteria encompassed studies involving RLT in lung NETs with efficacy and safety assessments. **Results:** Twenty-seven studies met the criteria, for a total of 786 patients. The pooled analysis revealed a 25.6% objective response rate and 75.6% disease control rate. Median progression-free survival averaged 20 months, while overall survival averaged 45 months. Factors affecting response included tumor burden, prior treatments, 18F-FDG PET scan uptake, and histological variants. RLT exhibited manageable grade 1/2 adverse effects, predominantly hematological, with Lu^{177} demonstrating a more favorable profile than Y^{90}. **Conclusion:** The findings support RLT's effectiveness in lung NETs, offering hope for advanced SSTR-positive patients. Although identifying predictive factors for response remains challenging, RLT retained efficacy even after prior therapies and typical carcinoids displayed a slightly better response than atypical ones.

Introduction

Neuroendocrine neoplasms (NENs) constitute a heterogeneous group of tumors, predominantly originating in the gastroenteropancreatic (GEP) tract and lungs [1–3]. Among the various treatment options that are available, one of the most effective and safest approaches for treating well-differentiated, unresectable/metastatic NENs with somatostatin receptor expression is the systemic administration of radiolabeled synthetic somatostatin analogs, known as radioligand therapy (RLT) or peptide-receptor radionuclide therapy (PRRT) [4]. The effectiveness of RLT for NEN treatment has been demonstrated in the Neuroendocrine Tumors Therapy (NETTER-1) trial, a phase 3 multicenter randomized controlled study. This study documented extended progression-free survival (PFS) in patients with midgut well-differentiated grade 1 or 2 neuroendocrine tumors (NETs), who received 177Lu-DOTATATE in combination with octreotide long-acting repeatable (LAR), as compared to those receiving high-dose octreotide LAR [5]. More recently, the results of the phase 3 NETTER-2 trial were presented at the 2024 ASCO Gastrointestinal Cancers Symposium [6]. This study investigated the efficacy and safety of 177Lu-DOTATATE as first-line treatment for advanced grade 2 or grade 3 GEP NETs (i.e., Ki-67 ≥10% and ≤55%). Compared to standard octreotide LAR, treatment with 177Lu-DOTATATE resulted in a significant extension of median progression-free survival (PFS) by 14.3 months, a notable increase (43.0% vs. 9.3%)in objective response rate (ORR), and a substantial 72.4% reduction in the risk of disease progression. With regards to lung NETs, the role of RLT with 177Lu-DOTATATE is still under investigation [7]. As expected, lung NETs express somatostatin receptor subtype 2 (SSTR-2), however the expression pattern may vary considerably, and only 44% of tumors display consistent and elevated SSTR expression on PET/CT scans [8]. These findings might imply that a majority of lung NETs would not be candidate for RLT. On the other hand, several real-world studies have demonstrated the effectiveness of RLT in the context of lung NETs, achieving results that are comparable to those of the NETTER-1 and

NETTER-2 trials, thus suggesting the applicability of RLT in this setting [9,10]. Current guidelines [1,11] recommend everolimus as second-line therapy in lung NETs after progression with somatostatin analogues (SSA) and relegate RLT as a possible third-line or fourth-line therapy. Therefore, there is a compelling need for urgent prospective trials to further investigate the potential benefits of RLT in the context of lung NET patients with positive uptake on somatostatin receptor imaging (SRI) who progressed despite treatment with SSA. While a phase II trial (NCT04665739) evaluating 177Lu-DOTATATE vs. everolimus in patients with advanced bronchial NETs and SSTR-positive imaging is currently underway, n this review we offer an extensive examination of already available data regarding the effectiveness and safety of RLT in individuals with lung NETs.

Materials and Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [12] (Supplemental Table 1). The review was not registered, and its protocol was not prepared.

Search strategy

A comprehensive search of English-language original articles was conducted on the MEDLINE and EMBASE database (the last search date was March 31, 2023). The search words were as follows: ((((peptide receptor radionuclide therapy AND lung carcinoid) OR (peptide receptor radionuclide therapy AND pulmonary carcinoid)) OR (peptide receptor radionuclide therapy AND bronchial carcinoid)) OR (peptide receptor radionuclide therapy AND bronchopulmonary carcinoid)) OR ((peptide receptor radionuclide therapy AND lung neuroendocrine tumor) OR (peptide receptor radionuclide therapy AND pulmonary neuroendocrine tumor) OR (peptide receptor radionuclide therapy AND bronchial neuroendocrine tumor) OR (peptide receptor radionuclide therapy AND bronchopulmonary neuroendocrine tumor)) OR ((radioligand therapy AND lung neuroendocrine tumor) OR

(radioligand therapy AND pulmonary neuroendocrine tumor) OR (radioligand therapy AND bronchial neuroendocrine tumor) OR (radioligand therapy AND bronchopulmonary neuroendocrine tumor)) OR ((radioligand therapy AND lung carcinoid) OR (radioligand therapy AND pulmonary carcinoid) OR (radioligand therapy AND bronchial carcinoid) OR (radioligand therapy AND bronchopulmonary carcinoid)).

Study selection

We selected all studies regarding the RLT treatment in lung carcinoid considering the following inclusion criteria: 1) prospective or retrospective study; 2) study population of more than 5 patients; 3) at least 1 cycle of PRRT treatment completed; 4) assessment of efficacy and safety outcomes. Seven authors independently screened all titles and abstracts and evaluated potentially eligible publications by retrieving full texts. Reviews, animal studies and case reports were excluded. The main reasons for exclusion were papers found to be not in English, not involving lung carcinoid or PRRT treatment, or lacking relevant data. Figure 1 depicts the flow diagram illustrating the study search algorithm.

Data extraction and quality assessment

Seven reviewers independently extracted the following data: study design (RCTs, prospective study, retrospective), age, sex, previous treatments, treatment schedule, outcomes of survival including PFS and overall survival (OS), predictive factors of response and adverse events. Studies with missing data or unclear information were excluded from further analysis. To evaluate treatment response for each study, we documented the percentage of patients achieving complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), assessed using widely employed radiological criteria such as Response evaluation criteria in solid tumors (RECIST), Southwest Cancer Chemotherapy Study Group (SWOG), or World Health Organization (WHO) standards. Table 1 shows the details of the included studies. Two authors (PM, TF) independently assessed the risk of bias for all studies on the basis of the National Heart, Lung, and Blood Institute of the National Institutes of

Health (NIH) for quality assessment for Before-After (Pre-Post) Studies With No Control Group [13] (Supplemental Table 2).

Results

Selected studies

Following the literature search, a total of 405 studies were initially identified as potentially relevant for our study. After a comprehensive screening process, only 27 studies, focusing on the utilization of RLT in patients with lung NET, met our inclusion criteria and were subsequently included. Figure 1 displays the outcomes of the literature search along with the reasons for article exclusion. The main features of the 27 articles are summarized in Table 1A and 1B. Twenty of these studies were retrospective analyses [14–33] and 7 studies were prospective analyses [34–40]. By including all the selected studies, a total of 786 patients underwent RLT, of which 756 had available data on therapy response. Gender distribution was not specified in all the studies but, where evaluated, male patients were more prevalent than females. The median age ranged from 44 to 70 years but it was indicated only in 12 out of 27 studies. The radionuclide administered was Y^{90} in 3 studies (total number of patients= 101), Lu^{177} in 13 studies (total number of patients= 327) and both Y^{90} and Lu^{177} in 10 studies (total number of patients= 243). One study investigated the efficacy and toxicity of Y^{90} alone (n= 45 patients), Lu^{177} alone (n= 48 patients) or both radionuclides (n=21 patients). When specified, the most common histological variants was the atypical carcinoid followed by the typical carcinoid, whereas histological variants other than typical and atypical carcinoids (i.e. small cell and large cell neuroendocrine carcinoma) were negligible. In the majority of studies patients were treated with previous systemic therapies before RLT and the RECIST version 1.1 criteria were considered to evaluate the response to treatment.

Evaluation of the response to RLT

As shown in Table 2, making an average of the response rates reported in the selected studies, the ORR was 25.6% (range 5.3-66.7%), while 50.0% of patients achieved SD (range 18.2-

83.3%). PD was 25.6% (range 0-46.7%). CR was a rare event, being reported only in three studies and three patients in total (Table 2). Comparing the response rates between the case series of patients treated with Lu^{177} alone or with Y^{90} and Lu^{177}, no substantial differences were observed with regard to ORR (24.9% vs 30.7%, respectively), SD (50.8% vs 48.5%, respectively) and PD (24.3% vs 20.8%, respectively). Despite the low number of studies (only 4) evaluating Y^{90}, the analysis of these patients showed similar mean percentages for ORR (22.1%) and SD (48.4%), whereas PD was more frequent (40.3%). Taking together these findings, RLT therapy allowed a disease control rate (DCR) of 75.6%.

Progression free survival and overall survival

Figure 1 indicates the PFS of the 13 studies with available data. On the average, the median PFS was 20.2 months with a minimum of 9.5 months [25] and a maximum of 32 months [23]. Only one study was performed by using the Y^{90} as radionuclide (median PFS= 23.1 months) [18], while the average median PFS was 24.1 months by using Lu^{177} and 15.2 months by using a combined Y^{90} and Lu^{177} RLT.

Data on OS are shown in Figure 3. These data were available in 18 studies and the median OS was 45.9 months, with a minimum of 26.9 months [30] and a maximum of 74.7 months [26]. Median OS was slightly higher in the case series of patients treated with Lu^{177} (roughly 50 months), as compared to those with either Y^{90} alone or Y^{90} and Lu^{177} (43 and 42 months, respectively).

Predictive factors of response and prognostic factors to RLT

Only limited data regarding predictors of response to RLT have been identified in the selected studies. Tumor burden, particularly the presence of liver metastases, was found to have a negative impact. In the study conducted by Sabet et al. [19], a hepatic tumor burden exceeding 50% was identified as a risk factor for shorter median PFS (32 months compared to 8 months in patients with a hepatic tumor burden $\leq$50%; p=0.008) and median OS (27 months compared to not reached in patients with a hepatic tumor burden $\leq$50%; p=0.009). Similarly,

in the study by Mariniello et al., patients presenting liver metastases exhibited a shorter OS compared to patients without liver metastases (HR= 3.31, 95% CI= 1.15-9.53; p= 0.03) [18]. However, in both studies these findings were not confirmed at multivariate analyses, indicating that liver metastases were not an independent risk factor for a worse outcome. Patients who received RLT after undergoing extensive prior treatments exhibited lower survival rates [18,33]. In the study conducted by Zhang et al., patients who showed no uptake on the 18F-FDG PET scan had better PFS and OS [27]. In relation to histotype, available data on the efficacy of RLT suggest a slightly better response in patients with typical compared to those with atypical carcinoid tumors. In the study conducted by Ianniello et al. [39], a DCR of 80% was achieved in patients with typical carcinoids, whereas in patients with atypical carcinoids, the rate was 47% (p=0.049). However, despite these findings, other studies such as those by Sabet [19] and Mirvis [28] did not find a significant association between typical/atypical histology and improved PFS or OS.

Toxicity profile

RLT was generally well-tolerated, with the majority of adverse effects (AEs) being grade 1/2 and only rarely grade 3/4. Renal injury and intestinal toxicity, such as nausea and diarrhea, were more frequently grade 1/2 [18,28,29]. The most common grade 3/4 AEs reported in the selected studies were related to hematological toxicity. In the study by Mariniello et al., anemia, leucopenia, or thrombocytopenia occurred in less than 5% of patients and only after treatment with either Y^{90} alone or Y^{90} and Lu^{177} [18]. Notably, no grade 3/4 AEs were recorded in patients treated with Lu^{177} alone. Similarly, in studies conducted by Iannello et al. and Parghane et al. [20,39], which investigated Lu^{177}, no grade 3/4 AEs were reported. Conversely, Sabet et al. [19] observed that grade 3 hematological toxicity occurred 3-10 weeks after at least one Lu^{177}cycle in 3 patients (13.6%). However, all patients recovered their blood count values within a mean time of 19 months after the therapy had ended.

Discussion

The recent findings of the NETTER-1 and NETTER-2 trials on patients with midgut NETs who received 177Lu-DOTATATE induced to consider this therapeutic option even in NET of different origin. Preliminary clinical data, mainly derived from retrospective single-institutional studies, suggest that RLT has potential applicability in managing any NET expressing SSTRs. The results from the recent SEPTRALU study indicated that RLT demonstrates effectiveness across various SSTR-expressing NENs, irrespective of their location, including subtypes other than midgut NENs [33]. To the best of our knowledge, there is only one ongoing clinical trial (NCT04665739) investigating 177Lu-DOTATATE in patients with lung NETs (estimated study completion in July 2024). While waiting for the results of this phase II trial, we conducted a comprehensive analysis of the published clinical studies focusing on effectiveness and safety of RLT in patients with lung NET.

We observed that RLT was effective in this setting; on average, the ORR was 25.6% with a DCR of 75.6%. PFS and OS were 20 and 45 months, respectively. Our observations were consistent with a recent meta-analysis of 177Lu-DOTATATE in pulmonary NETs [10]. This study conducted by Ma et al. included 5 research papers in quantitative synthesis and concluded that the pooled disease response rate was 0.24 (95% CI, 0.15-0.32) and the pooled DCR was 0.77 (95% CI, 0.62-0.92). Moreover, the pooled PFS was 21.59 months (95% CI: 17.65-25.53 months), and the pooled OS was 48.78 months (95% CI: 41.00-56.57 months). The high degree of overlap between findings from the above mentioned metanalysis and the present study reinforce the robustness of the efficacy data of RLT in lung NET, even though a prospective trial has not available at now in this field. As compared to the metanalysis, the present review also considers studies with 90Y and combination therapy Y^{90} and Lu^{177}, as well as includes small series and some recent large studies such as a Spanish national registry study collecting 56 lung NETs [33]. So, in spite of increasing the heterogeneity of study population and study design, the performance data remain constant with this kind of therapy in patients with lung NETs.

In the majority of the studies reviewed, patients had received prior therapies before RLT, and the results consistently showed sustained efficacy of RLT even in these cases. However, further investigation is required to ascertain the optimal timing of RLT in lung NETs. Consistent with the findings of the NETTER-2 trial, where RLT was administered as a first-line treatment, it remains to be determined whether initiating RLT at an earlier disease stage offers significant benefits for patients. Nevertheless, current evidence suggests that when conventional treatment options were exhausted, RLT remained effective.

Hence, RLT emerges as a promising therapeutic avenue for patients with lung NETs. However, predicting the response to RLT presents challenges, and identifying factors associated with a better treatment response may steer the selection of patients poised to benefit from this treatment. This selection process has been studied, for example, in patients with gastroenteropancreatic NENs [41]. Regrettably, there are few studies addressing this aspect specifically for patients with bronchopulmonary NETs. Among the considerations, patients theoretically poised for a better response might have a lower tumor burden, exhibit no uptake on the 18F-FDG PET scan, and have not received prior systemic therapies [18,19,27,33]. While patients with typical carcinoids exhibit a more favorable response profile compared to those with atypical carcinoids, current data indicate that this distinction does not result in a significant improvement in survival outcomes. Whether this phenomenon is primarily associated with a presumably lower rate of SSTR expression in atypical carcinoids or involves other relevant biological distinctions remains a subject for further investigation. Consequently, this selection criteria might limit RLT's availability to a restricted group of patients, and it remains uncertain whether patients not meeting these criteria could obtain the same level of benefit. Notably, while RLT demonstrates efficacy in enhancing both PFS and OS, studies also report a significant improvement in patients' quality of life [42].

RLT administered to patients with lung NETs has shown a commendable safety profile. The primary adverse effects commonly observed were associated with hematological toxicities, aligning with the findings from the NETTER-1 trial conducted on patients with midgut NENs. When comparing the two radionuclides utilized in the selected studies, Lu^{177} exhibited a more favorable toxicity profile compared to Y^{90}. Despite 177Lu-DOTATATE being the sole treatment approved by the FDA and EMA, several trials—both completed and ongoing—are investigating the efficacy of Y^{90} in treating NETs. Many of the studies chosen for this review were conducted prior to the NETTER-1 trial results, during a time when RLT was not a standard option and predicting and managing AEs might have been less predictable. Currently, our understanding and ability to prevent, identify, and address these AEs have notably advanced. As a result, it is plausible to anticipate that both radionuclides exhibit similar toxicity profiles.

The current scenario in RLT mirrors the historical observations made with SSA therapy [43]. The results from the PROMID [44] and CLARINET [45] studies demonstrated the effectiveness of SSA in patients with midgut NETs. However, there's a notable absence of randomized clinical trials validating these outcomes for lung carcinoid patients. The SPINET trial was prematurely concluded due to slow participant enrollment. In this trial individuals diagnosed with SSTR-positive typical and atypical carcinoids were randomized to receive either lanreotide LAR 120 mg (n=51) or a placebo (n=26) administered every four weeks. The findings, presented at the 2021 ESMO meeting [46], indicated a PFS of 21.9 months for lanreotide compared to 13.9 months for placebo among individuals with typical carcinoids. For those with atypical carcinoids, the PFS was 13.8 months for lanreotide versus 11.0 months for placebo. Researchers inferred that administering lanreotide at 120 mg dosage every 4 weeks might serve as a potential treatment strategy, especially for those diagnosed with typical carcinoids. Despite lacking approval from the Food and Drug Administration, SSA is frequently employed as first-line therapy for lung carcinoids. Further investigation is

warranted to determine whether extending the use of SSA treatment from midgut NETs to lung carcinoids will similarly extend the therapeutic indications for RLT in patients with lung carcinoids.

This systematic review is constrained by various limitations primarily stemming from the heterogeneity among the selected studies and the absence of significant prospective randomized trials. Consequently, deriving definitive conclusions or conducting comprehensive statistical analyses presents a challenge.

In conclusion, the decision to use RLT for lung NETs mainly depends on various factors, including tumor characteristics, STTRs expression, tumor stage and grade, and the patient's performance status. Research on this area is ongoing, however, based on the existing data, experienced multidisciplinary teams may contemplate RLT as a potential off-label option, alongside everolimus and other treatment choices, for patients with advanced, SSTR-positive lung typical/atypical NETs that show progression while on SSAs.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

PM, AF and AC contributed to the conception of the study. PM, TF, NM, GC, SDM, BA, CM analyzed the literature databases and extrapolated useful articles. PM, TF, NM, GC, SDM, BA, CM performed the

309 data analyses. PM, TF, NM, GC, AF wrote the article. PF, AF, AC contributed to article
310 supervision.
311

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Figure Legends

Fig. 1. PRISMA flow chart of literature search results.

Fig. 2. Median progression free survival (PFS) and 95% confidence intervals of the selected studies.

Fig. 3. Median overall survival (OS) and 95% confidence intervals of the selected studies.