Review

Peptide Receptor Radionuclide Therapy for Patients With Advanced Lung Carcinoids

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Abstract

Neuroendocrine neoplasms (NEN) are a family of malignancies of diverse origin, including the lung, gastrointestinal tract, and pancreas. Lung NEN include well differentiated neuroendocrine tumors (NET) classified as typical carcinoids or atypical carcinoids, and poorly differentiated neuroendocrine carcinomas classified as small-cell lung carcinoma or large-cell neuroendocrine carcinoma. According to a recent analysis of a large, population-based registry, approximately one-third of all patients with lung typical/atypical carcinoids have distant metastases at diagnosis, and median survival for these patients is 24 months. At present, only 1 therapy is approved by the US Food and Drug Administration (FDA) for patients with advanced lung typical/atypical carcinoids, everolimus, indicating a clear need for more treatment options in this patient population. Although not yet supported by results from randomized prospective trials, somatostatin analogues are considered an acceptable treatment option for patients with lung typical/atypical carcinoids expressing somatostatin receptors. Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE was recently approved by the FDA for the treatment of gastroenteropancreatic NET; however, the role of PRRT in patients with lung typical/atypical carcinoids remains unclear, because they were not included in the pivotal NETTER-1 (Neuroendocrine Tumors Therapy) trial. Herein we provide a comprehensive review of the available clinical evidence for efficacy and safety of PRRT in patients with lung typical/atypical carcinoids. On the basis of the preliminary evidence of efficacy and the consistent safety profile in this patient group, we propose that experienced multidisciplinary NET teams may consider PRRT alongside everolimus as an option for patients with advanced somatostatin receptor-positive lung typical/atypical carcinoids whose disease is progressing during first-line treatment with somatostatin analogues.

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Introduction to Lung Typical and Atypical Carcinoids

Lung Typical and Atypical Carcinoids Are Subtypes of Lung Neuroendocrine Neoplasms

Lung neuroendocrine neoplasms (NEN) are divided into 4 subtypes according to the World Health Organization (WHO) classification.[1] Lung typical carcinoids and atypical carcinoids, which are well differentiated and might be collectively referred to as lung neuroendocrine tumors (NET), are by definition low-grade and intermediate-grade tumors, respectively.[1] Large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC) are poorly differentiated neoplasms that might be collectively referred to as lung neuroendocrine carcinomas and are both high-grade tumors[1]; these tumors are beyond the scope of this review. Herein we present a comprehensive review of the available clinical evidence for the efficacy and safety of peptide receptor radionuclide therapy (PRRT) in patients with lung typical/atypical carcinoids.

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Incidence, Stage at Diagnosis, and Survival of Patients With Lung Typical/Atypical Carcinoids

The lung is the most common primary site of NEN, with lung typical/atypical carcinoids accounting for approximately 25% of all newly diagnosed NEN (Surveillance, Epidemiology, and End Results [SEER], 2000-2012), with an incidence of 1.49 per 100,000 persons.[2] The median survival in patients with lung typical

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carcinoids and atypical carcinoids in the SEER registry was 201 and 101 months, respectively.[3] Recent data from the SEER database (2000-2012) indicate a median survival of 24 months and a 5-year survival rate of 32% in patients diagnosed with distant spread of lung typical/atypical carcinoids.[2] Registry studies such as SEER have substantial limitations, including lack of central pathology review and lack of treatment data. Moreover, treatment options and therapy patterns as well as diagnostic methods have changed substantially during the observation period, and therefore the observed survival might not accurately reflect current outcomes.

Histopathologic Classification of Lung Typical/Atypical Carcinoids

The distinction between lung NEN subtypes can be made by evaluating mitotic index, degree of necrosis, Ki-67 index, cell morphology, and other parameters.[1] Necrosis is typically extensive in LCNEC and SCLC, focal or absent in atypical carcinoids, and absent in typical carcinoids.[1] A higher number of mitoses and the presence of necrosis are considered the defining features for atypical (2-10 per 2 mm^2) versus typical (0-1 per 2 mm^2) carcinoids.[1] Although its use in discriminating typical from atypical carcinoids is not established,[1] the Ki-67 index clearly has prognostic value.[4,5] Typical carcinoids have Ki-67 of up to 5%, atypical carcinoids have Ki-67 of up to 20%, LCNEC have Ki-67 of 40% to 80%, and SCLC have Ki-67 of 50% to 100%.[1] Recently, outcomes of patients with well differentiated lung NET with Ki-67 >20% were assessed.[6] Although these tumors share morphologic and immunohistochemical (IHC) features with well differentiated NEN that have Ki-67 ≤20%, their outcome is inferior.[6] Other grading systems for lung NET have been proposed but await validation.[7]

Symptoms of Lung Typical/Atypical Carcinoids

Because of the varying presentation of symptoms, lung typical/atypical carcinoid diagnosis can be challenging.[8] Patients with centrally located lung typical/atypical carcinoids generally have respiratory symptoms, whereas peripheral lung typical/atypical carcinoids are often discovered incidentally.[9] Common presenting symptoms in patients with lung typical/atypical carcinoids include cough, hemoptysis, dyspnea, and chest pain.[10-12] Some patients are asymptomatic and might present with a lung mass detected on radiography performed for other reasons.[13]

Somatostatin Receptors and Somatostatin Receptor-Based Imaging in Gastroenteropancreatic NET

Most studies on somatostatin receptor (SSTR) expression in NET have been undertaken in patients with gastroenteropancreatic (GEP) primary sites. GEP NET overexpress SSTRs, with the expression level of each SSTR subtype appearing to differ according to primary tumor location or functional tumor type.[14] Overall, IHC expression by GEP NET has been reported to be 68% for SSTR1, 86% for SSTR2, 46% for SSTR3, 93% for SSTR4, and 57% for SSTR5.[14] Studies have shown that the presence of SSTRs can easily be assessed with IHC staining and that there is good interlaboratory and interobserver agreement regarding IHC results.[15] The presence of SSTRs detected in IHC studies appears to correlate with findings of receptor-based imaging studies and predict outcomes of SSTR-targeted therapy in patients with NET.[16-20] On the basis of the high expression of SSTR2 in GEP NET, SSTR scintigraphy (SRS) with ^{111}In-pentetreotide has been a commonly used technique for imaging the tumors, with this radiopharmaceutical having a high affinity for SSTR2 (see Supplemental Figure 1 in the online version).[21-23] GEP NET detection rates reported with SRS using ^{111}In-pentetreotide are >75%.[24] Positron emission tomography (PET) with Gallium-68-labeled agents DOTATATE, DOTATOC, and DOTANOC have recently replaced SRS as the method of choice for SSTR imaging in patients with NET because of the higher resolution and therefore greater diagnostic accuracy of PET, along with lower radiation dose and improved patient convenience.[21,24-27] All 3 agents bind with high affinity to SSTR2A; in addition, DOTATOC binds to SSTR5, and DOTANOC binds to SSTR3 and SSTR5.[21] Beyond its role in the diagnosis and staging of tumors, SSTR-based imaging is important for the assessment of eligibility of patients with GEP NET for treatment with somatostatin analogues (SSAs) and PRRT, which act on SSTR.[9,24] In the landmark NETTER-1 (Neuroendocrine Tumors Therapy) trial of PRRT in patients with midgut NET, a key inclusion criterion was the presence of SSTRs on the surface of the tumor cells manifested as uptake more than or equal to normal background liver uptake observed on planar imaging.[28] Recent guidelines have addressed the topic of imaging in patients with NET, but there is not a universally agreed upon standard for reporting uptake seen on receptor imaging.[24] A commonly used scoring system is the Krenning score, designed to be used for SRS.[29] Although this scoring system is commonly applied to DOTATATE PET imaging, it has not been appropriately validated.[29,30] Caution must be taken to apply SRS criteria used in NETTER-1 to SSTR PET imaging.[30]

Somatostatin Receptors and SSTR Imaging in Lung Typical/Atypical Carcinoids

Few studies have examined SSTR expression in lung typical/atypical carcinoids. One study reported positive SSTR2A expression according to IHC in approximately 66% of typical carcinoids, approximately 74% of atypical carcinoids, and 82% of metastatic lesions in patients with lung typical/atypical carcinoids.[31] Primary lung typical/atypical carcinoids and metastatic lesions were also shown to express SSTR1 (approximately 60% and 82%, respectively), SSTR3 (approximately 21% and 35%), and SSTR5 (approximately 40% and 59%) proteins.[31] Concordance in SSTR2A and SSTR5 IHC staining between metastatic lesions and the corresponding primary lung tumor was shown for 88%.[31] For the few studies available, a median tumor detection rate of 90% (range, 79%-100%) with Gallium-68 PET imaging of patients with lung typical/atypical carcinoids has been reported (see Supplemental Figure 2 in the online version).[10,32-39] Use of Gallium-68 SSTR-based PET alongside ^{18}F-fludeoxyglucose (FDG) PET, a measure of tumoral glycolytic activity, has been suggested for NET with Ki-67 >10% for its prognostic value.[40,41] FDG PET generally shows a higher uptake in lung atypical carcinoids than in typical carcinoids,[9,42] and increased FDG uptake might correlate with worse progression-free survival (PFS) in lung typical/atypical carcinoids.[42,43]

Introduction to PRRT

Peptide Receptor Radionuclide Therapy Agents

Yttrium-90 or Lutetium-177 are bound to DOTATATE or DOTATOC to selectively target SSTR-positive cells in NET using PRRT (Figure 1).[22,44,45] Radioactive decay of Yttrium-90 or Lutetium-177 leads to cell death in NET. Yttrium-90 is a β-negative (β^-) emitter, with a maximum β^- particle range of 11 mm and a half-life of 2.7 days.[44] Lutetium-177 is an emitter of β^- and γ, with a maximum β^- particle range of 2 mm and a half-life of 6.7 days.[44] On the basis of the particle range of Yttrium-90, the potential for toxicity to adjacent healthy tissue is greater when Yttrium-90 is used compared with Lutetium-177.[46] ^{177}Lu-DOTATATE (Lutathera; Advanced Accelerator Applications USA, Inc, Millburn, NJ) was recently approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the treatment of advanced $SSTR^+$ GEP NET.[45,47] A summary of the PRRT protocols used at the Mayo Clinic and the Banner M.D. Anderson Cancer Center are provided in Supplemental Appendices 1 and 2 in the online version, respectively. Details of the administration protocol at the Dana-Farber Cancer Institute were provided in a recent article.[48]

Patient Eligibility Criteria for PRRT According to the European Neuroendocrine Tumor Society 2017 Guidelines

The European Neuroendocrine Tumor Society (ENETS) 2017 guidelines were developed after the publication of the NETTER-1 study, which reported favorable outcomes in patients with NET treated with ^{177}Lu-DOTATATE. Patients eligible for PRRT treatment must have inoperable/metastatic well differentiated (Grade1/2) NET, sufficient tumor uptake on SSTR-based imaging, sufficient bone marrow reserves (Grade1-2 hematologic toxicity usually accepted), creatinine clearance >50 mL per minute, Karnofsky performance status >50%, and expected survival >3 months.[49] PRRT is not indicated for patients with significant sites of active disease lacking SSTR expression, which can be confirmed by increased uptake on FDG PET/computed tomography imaging.[49] Contraindications include pregnancy, severe hepatic or cardiac impairment, and significant bone marrow dysfunction manifested by cytopenias.[49]

Peptide Receptor Radionuclide Therapy Treatment Scheme According to the ENETS 2017 Guidelines

No strict guidelines can be provided for PRRT treatment schemes because no randomized clinical trials are available that establish optimal administered activity per treatment cycle, optimal cycle interval, or optimal cumulative administered activity.[49] Variation in PRRT administration is on the basis of tumor burden, extent of bone marrow involvement, renal function, and perhaps body habitus.[49]

Peptide Receptor Radionuclide Therapy Administration According to Lutathera Prescribing Information

The recommended dose of ^{177}Lu-DOTATATE is 7.4 GBq (200 mCi) ±10% every 8 weeks for a total of 4 doses.[45] Long-acting SSAs should not be administered for at least 4 weeks before ^{177}Lu-DOTATATE and may be administered between 4 and 24 hours after each ^{177}Lu-DOTATATE dose.[45] Administration of an intravenous (I.V.) amino acid solution containing L-lysine and L-arginine should be initiated 30 minutes before administering ^{177}Lu-DOTATATE and continued during ^{177}Lu-DOTATATE infusion and for at least 3 hours afterward.[45] This amino acid solution is essential to protect kidneys from possible radiation-related side effects.[45] Commercially available amino acid solutions should be used only if they have an osmolarity <1050 mOsmol.[45,47]

Clinical Efficacy and Safety of PRRT in NET on the Basis of NETTER-1

To date, the only randomized controlled trial of PRRT in patients with NET is the NETTER-1 study, which examined the efficacy and safety of ^{177}Lu-DOTATATE in patients with advanced midgut NET and radiologic progressive disease (PD) while they were receiving a standard dose of long-acting octreotide.[28] Patients with primary lung typical/atypical carcinoids were not included in this trial. At the time of primary end point analysis (median follow-up, 14 months) the median PFS had not yet been reached in the group receiving ^{177}Lu-DOTATATE (plus continued long-acting octreotide) and was 8.4 months in the control group receiving a high dose (60 mg) of long-acting octreotide, which represented a 79% lower risk of disease progression or death with PRRT.[28] Tumor response in terms of objective response rate (ORR) was 18% in the ^{177}Lu-DOTATATE group and 3% in the group receiving 60 mg long-acting octreotide; 1 complete response (CR), and 17 partial responses (PRs) occurred in the group receiving PRRT, and 3 PRs occurred in the control group.[28] Treatment-related adverse events (AEs) occurred in 86% of patients receiving PRRT (serious in 9%) versus 31% in the control group (serious in 1%).[28] The most common AEs among patients in the ^{177}Lu-DOTATATE group were nausea and vomiting, which were generally associated with amino acid infusions that patients also received, and which resolved after completion of the infusions.[28] Hematologic AEs were transient, and there was no evidence of renal toxic effects during the median follow-up of 14 months.[28] The NETTER-1 study also showed a significant quality of life (QoL) benefit for patients with midgut NET who received ^{177}Lu-DOTATATE versus those treated with high-dose long-acting octreotide.[50]

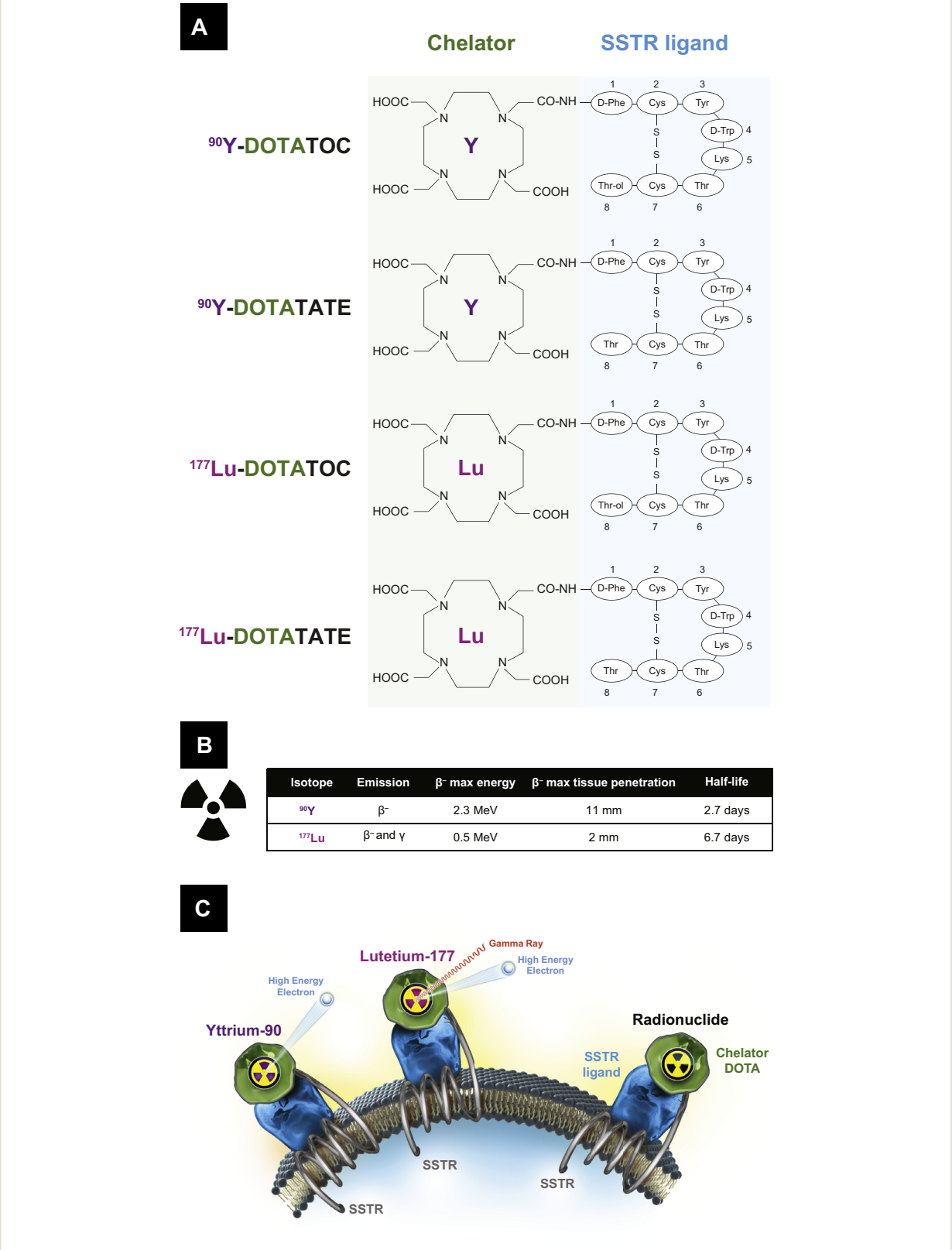
Long-Term Safety of PRRT in Patients With NEN

Subacute hematologic toxicity (Grade3/4) after PRRT with ^{177}Lu-DOTATATE occurs in 11% of patients.[51] Long-term safety concerns with PRRT include myelodysplastic syndrome (MDS) and leukemia.[52] Two large retrospective studies of 610 and 1048 patients, respectively, have recently reported the development of these toxicities in 2% of NEN patients treated with PRRT.[53,54] Brabander et al reported that MDS (1.5%) and acute leukemia (0.7%) occurred after a median follow-up of 28 (range, 9-41) months and 55 (range, 32-125) months, respectively, after first PRRT.[54]

Clinical Studies of PRRT in Patients With Lung Typical/Atypical Carcinoids

Because patients with lung typical/atypical carcinoids were not included in the NETTER-1 trial, it is unclear whether these PRRT

Figure 1 Peptide Receptor Radionuclide Therapy Agents: (A) Chemical Structure, (B) Emissions, and (C) Mechanism of Binding to Neuroendocrine Tumor Cells. Data from Fani et al,[22] Bodei et al,[44] and the Lutathera package insert[45]



Isotope	Emission	β⁻ max energy	β⁻ max tissue penetration	Half-life
^{90}Y	β⁻	2.3 MeV	11 mm	2.7 days
^{177}Lu	β⁻ and γ	0.5 MeV	2 mm	6.7 days

Abbreviation: SSTR = somatostatin receptor.

results could be extrapolated to patients with advanced, progressing lung typical/atypical carcinoids. However, on the basis of its mechanism of action, it is likely that PRRT will be active in any SSTR-expressing NET, including patients with lung typical/atypical carcinoids. To our knowledge, no patients with lung typical/atypical carcinoids have been included in a phase III randomized clinical trial on PRRT efficacy. However, phase II, phase I/II, phase I, and other prospective and retrospective studies provide preliminary evidence of PRRT efficacy in patients with lung typical/atypical carcinoids.

We conducted a literature search of the PubMed and Cochrane Libraries for relevant articles published between January 1, 2000, and April 12, 2018 using the following search terms: peptide receptor radionuclide therapy OR radioisotope therapy OR dotatate OR dota-tate OR octreotate OR lutathera OR DOTA-Tyr3-octreotate OR DOTA0-Tyr3-Octreotate OR dotatoc OR dota-toc OR dota-octreotide OR DOTA-Tyr3-octreotide OR DOTA0-Tyr3-Octreotide OR edotreotide AND neuroendocrine OR carcinoid AND bronchopulmonary OR pulmonary OR bronchial OR lung OR thoracic. Conference databases from the American Society of Oncology, the European Society for Medical Oncology, North American Neuroendocrine Tumor Society, the ENETS, the American Association for Cancer Research, the American Thoracic Society, the European Association of Nuclear Medicine, the Endocrine Society, the International Association for the Study of Lung Cancer, and the Society of Nuclear Medicine and Molecular Imaging were searched for relevant abstracts presented between 2016 and 2018.

Studies with an exclusive focus on patients with lung typical/atypical carcinoids include 1 phase II trial[42] and 4 single/dual-institution retrospective analyses.[55-58] Four other phase II trials have reported outcomes for a subgroup of patients with lung typical/atypical carcinoids,[59-62] ranging from 3 patients[62] to 84 patients.[60] The outcomes of these and other relevant studies are detailed in the following sections.

Efficacy Outcomes: Tumor Response/Survival With ^{177}Lu-DOTATATE

Seven studies have reported tumor response and survival outcomes for patients with lung typical/atypical carcinoids who have received ^{177}Lu-DOTATATE (Table 1).[42,54,57,58,63-65] Three of these studies focused exclusively on patients with lung typical/atypical carcinoids.[42,57,58] Among the studies, ORR ranged from 15% to 80% (median value, 30%) and the disease control rate (DCR) ranged from 61% to 100% (median value, 68%). Heterogeneity in patient populations, small size of the study populations, and varying tumor response criteria might explain the differences in the reported ORR and DCR.

Two studies of ^{177}Lu-DOTATATE reported efficacy outcomes for the overall patient population with lung typical/atypical carcinoids and separately for subgroups with typical carcinoids and atypical carcinoids.[42,57] A prospective phase II trial of 34 patients with progressive, metastatic bronchial typical/atypical carcinoids reported an ORR of 15% with ^{177}Lu-DOTATATE, consisting of 1 CR and 4 PRs.[42] The 5 objective responses occurred in patients with typical carcinoids, whereas none occurred in those with atypical carcinoids.[42] A DCR of 62% was achieved in the overall patient population, with a DCR of 80% in patients with typical carcinoids and 47% in those with atypical carcinoids.[42] Overall, patients with lung typical/atypical carcinoids had a median PFS of 18.5 months and overall survival (OS) of 48.6 months; patients with typical carcinoids had a median PFS of 20.1 months and OS of 48.6 months; and patients with atypical carcinoids had a median PFS of 15.7 months and OS of 37.0 months.[42] A retrospective study by Sabet et al of 22 patients with metastatic pulmonary typical/atypical carcinoids (77% with baseline PD) reported a DCR of 68% with ^{177}Lu-DOTATATE, with a DCR of 80% in those with typical carcinoids and 65% in those with atypical carcinoids.[57] Overall, patients with lung typical/atypical carcinoids had a median PFS of 27 months and OS of 42 months; patients with typical carcinoids had a median PFS of 29 months and OS of 42 months; and patients with atypical carcinoids had a median PFS of 26 months and OS of 35 months.[57] The findings from these 2 studies might indicate that the underlying biology of individual tumors plays a role in the response to this treatment modality, with greater efficacy of PRRT in typical carcinoids than in atypical carcinoids, but these results need to be verified in larger prospective randomized studies.

Efficacy Outcomes: Tumor Response/Survival With ^{90}Y-DOTATOC

Limited data on the efficacy of ^{90}Y-DOTATOC have been reported in 4 clinical trials that included patients with lung typical/atypical carcinoids as a subgroup of a larger patient population, including 3 phase II trials and 1 phase I trial (Table 2).[60-62,66] A 100% DCR was reported for patients with lung typical/atypical carcinoids in the 3 studies using WHO tumor response criteria, with the ORR ranging from 0% to 50%. The efficacy of ^{90}Y-DOTATOC in patients with lung typical/atypical carcinoids requires verification in further studies.

Efficacy Outcomes: Tumor Response/Survival With ^{177}Lu- and/or ^{90}Y-labeled PRRT Agents

Six further studies have reported efficacy in patients with lung typical/atypical carcinoids who had received ^{177}Lu- and/or ^{90}Y-labeled PRRT agents (Table 3).[53,55,56,59,67,68] One of these studies was a phase II clinical trial, and the others were retrospective studies. Two studies focused exclusively on patients with lung typical/atypical carcinoids.[55,56] The most comprehensive efficacy data were from the retrospective study by Mariniello et al, which included 114 patients with advanced bronchopulmonary typical/atypical carcinoids.[55] This study showed an efficacy advantage of PRRT with ^{177}Lu-DOTATATE compared with ^{90}Y-DOTATOC, in terms of the ORR, DCR, median PFS, and median OS. Furthermore, the hazard ratio (HR) for death and disease recurrence was reported to be higher with ^{90}Y-DOTATOC than with ^{177}Lu-DOTATATE (death HR, 2.0 [95% confidence interval (CI), 1.2-4.2], $P = .014$; disease recurrence HR, 1.55 [95% CI, 1.01-2.03], $P = .04$). Consistent with efficacy outcomes for ^{177}Lu-DOTATATE alone in the studies by Ianniello et al[42] and Sabet et al,[57] an overall PRRT (pooled data for all PRRT agents) benefit was reported in patients with typical carcinoids compared with atypical carcinoids (for atypical vs. typical carcinoids: death HR, 2.17 [95% CI, 1.1-4.44], $P = .034$; disease recurrence HR, 2.86 [95% CI, 1.35-6.07], $P = .006$).

Table 1 Tumor Response and Survival in Studies Reporting ^{177}Lu-DOTATATE PRRT Outcomes for Patients With Lung TC/AC

PRRT Agent	Type of Study	Reference	Total Patient Group	Relevant Patient Group With Treatment Outcome	Response Criteria	CR	PR	MR	SD	PD	ORR	DCR	PFS	OS
						n (%)							Median in Months (95% CI)	
^{177}Lu-DOTATATE	Phase II	Ianniello et al[42]	Metastatic bronchial TC/AC with baseline PD and SRS$^+$ (n = 34)	Total (n = 34)	SWOG	1 (3)	4 (12)	NA	16 (47)	13 (38)	5 (15)	21 (62)	18.5 (12.9-26.4)	48.6 (26.4-68.9)
				TC (n = 15)		1 (6)	4 (27)		7 (47)	3 (20)	5 (33)	12 (80)	20.1 (11.8-26.8)	48.6 (26-NR)
				AC (n = 19)		0	0		9 (47)	10 (53)	0	9 (47)	15.7 (10.6-25.9)	37.0 (18.7-68.9)
	Phase I/II	Bodei et al[63]	Unresectable or metastatic SRS$^+$ tumors (n = 51);76% with baseline PD	Bronchial TC/AC (n = 5)	RECIST with MR (▼ <30%)	0	2 (40)	2 (40)	1 (20)	0	4 (80)	5 (100)	NS	NS
	Prospective	Garske-Roman et al[64]	Metastatic NET with SRS$^+$ (n = 200)	Lung TC/AC (n = 6); 4/6 had baseline PD	RECIST version 1.1	0 (0)	1 (17)	NA	5 (83)	0 (0)	1 (17)	6 (100)	18 (12-43)	NR (19-NR)
	Retrospective	Sabet et al[57]	Metastatic WD pulmonary TC/AC with SSTR$^+$ imaging (n = 22); 77% with baseline PD	Total (n = 22)	RECIST version 1.1	0	6 (27)	NA	9 (41)	7 (32)	6 (27)	15 (68)	27 (9-45)	42 (25-59)
				TC (n = 5)		0	NR		NR	1 (20)	NR	4 (80)	29 (9-49)	42 (24-60)
				AC (n = 17)		0	NR		NR	6 (35)	NR	11 (65)	26 (6-47)	35 (NA)
	Retrospective	Parghane et al[58]	Advanced pulmonary NEN with SSTR$^+$ imaging (n = 22); TC (n = 13), AC (n = 8) and SCLC (n = 1)	Total evaluable (n = 19)	RECIST version 1.1 with MR (▼ 10%-30%)	1 (5)	1 (5)	4 (21)	7 (37)	6 (32)	6 (32)	13 (68)	NS	40 (NS)
	Retrospective	Brabander et al[54]	GEP NET or bronchial TC/AC with SRS$^+$ (n = 443); 54% with baseline PD	Bronchial TC/AC (n = 23)	RECIST version 1.1	0 (0)	7 (30)	NA	7 (30)	6 (26)	7 (30)	14 (61)	20 (NS)	52 (49-55)
	Retrospective	van Essen et al[65]	Metastatic bronchial/thymic TC/AC or gastric NET with SRS$^+$ (n = 16)	Bronchial TC/AC (n = 9); 2/9 had baseline PD, 5/9 had unknown status	SWOG with MR (▼ ≥25% and <50%)	0	5 (56)	1 (11)	2 (22)	1 (11)	6 (67)	8 (89)	TTP 31 (NS)	NS

Abbreviations: AC = atypical carcinoids; DCR = disease control rate (including CR, PR, minor response [if applicable], and SD); GEP = gastroenteropancreatic; MR = minor response; NEN = neuroendocrine neoplasms; NET = neuroendocrine tumors; NR = not reached; NS = not stated; OS = overall survival; PFS = progression-free survival; PRRT = peptide receptor radionuclide therapy; RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small-cell lung carcinoma; SRS = somatostatin receptor scintigraphy; SSTR = somatostatin receptor; SWOG = Southwest Oncology Group; TC = typical carcinoids; TTP = time to tumor progression; WD = well differentiated.

Table 2 Tumor Response and Survival in Studies Reporting ^{90}Y-DOTATOC PRRT Outcomes for Patients With Lung TC/AC

PRRT Agent	Type of Study	Reference	Total Patient Group	Relevant Patient Group With Treatment Outcome	Response Criteria	n (%)							Median in Months (95% CI)	
						CR	PR	MR	SD	PD	ORR	DCR	PFS	OS
^{90}Y-DOTATOC	Phase II	Imhof et al[60]	Metastatic NET with baseline PD and SRS^{+} (n = 1109)	Bronchial TC/AC (n = 84)	Nonstandard	NS	NS	NS	NS	NS	NS	NS	NS	Mean 40 (31-50)
	Phase II	Waldherr et al[62]	GEP NET or bronchial TC/AC with baseline PD and SSTR^{+} imaging (n = 39)	Bronchial TC/AC (n = 3)	WHO	0	0	NA	3 (100)	0	0	3 (100)	NS	NS
	Phase II	Waldherr et al[61]	NET with baseline PD and SSTR^{+} imaging (n = 41)	Bronchial TC/AC (n = 7)	WHO	1 (14)	1 (14)	NA	5 (71)	0	2 (29)	7 (100)	NS	NS
	Phase I	Bodei et al[66]	Tumors with SSTR^{+} imaging and baseline residual disease or PD (n = 40)	Lung TC/AC (n = 2)	WHO	0	1 (50)	NA	1 (50)	0	1 (50)	2 (100)	NS	NS

Abbreviations: AC = atypical carcinoids; DCR = disease control rate (including CR, PR, minor response [if applicable], and SD); GEP = gastroenteropancreatic; MR = minor response; NET = neuroendocrine tumor; NS = not stated; OS = overall survival; PFS = progression-free survival; PRRT = peptide receptor radionuclide therapy; SRS = somatostatin receptor scintigraphy; SSTR = somatostatin receptor; TC = typical carcinoids; WHO = World Health Organization.

Efficacy Outcomes: Survival for Lung NEN Versus Other Primary Sites

A large retrospective study examined survival outcomes according to NEN primary site and showed that patients with lung NEN have a shorter median PFS and OS with PRRT (all agents) than patients with panNEN and NEN originating in the small bowel (Figure 2).[53] However, a limitation of this study is that it included patients with NEN of all grades, rather than patients with lung typical/atypical carcinoids specifically; therefore, data from patients with SCLC or LCNEC might have influenced survival reported for this subgroup. The shorter OS observed in patients with lung NEN versus midgut and pancreatic primary sites is supported by another large retrospective study of 419 patients with NET who received ^{177}Lu-DOTATATE.[54] Median OS was 52 months (95% CI, 49-55) for bronchial typical/atypical carcinoids, 71 months (95% CI, 56-86) for pancreatic neuroendocrine tumors (panNET), and 60 months (95% CI, 52-68) for midgut NET.[54]

Efficacy Outcomes: Symptom Control

To our knowledge, no studies have primarily aimed to assess control of functional symptoms with PRRT in patients with lung typical/atypical carcinoids. In the 5 studies of PRRT that specifically focused on patients with lung typical/atypical carcinoids, examination of the baseline patient characteristics revealed that up to 68% of patients had carcinoid syndrome or other functional symptoms (Table 4).[42,55-58] Evidence of functional symptom improvement was reported in 3 studies[56-58] and did not appear to be examined in the other 2 studies.[42,55]

Efficacy Outcomes: QoL

To our knowledge, only 1 study has examined QoL in patients with lung typical/atypical carcinoids receiving PRRT, who were included in the study as part of a large group of patients with GEP NET or lung typical/atypical carcinoids.[69] QoL results were reported for the entire patient population rather than for those with lung typical/atypical carcinoids specifically.[69] The study showed a significant improvement in European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire general health status with ^{177}Lu-DOTATATE and no significant worsening of QoL in patients who had no symptoms before therapy.[69] These results appear to be consistent with those reported from the NETTER-1 study of patients with a midgut primary site.[50]

Safety Outcomes

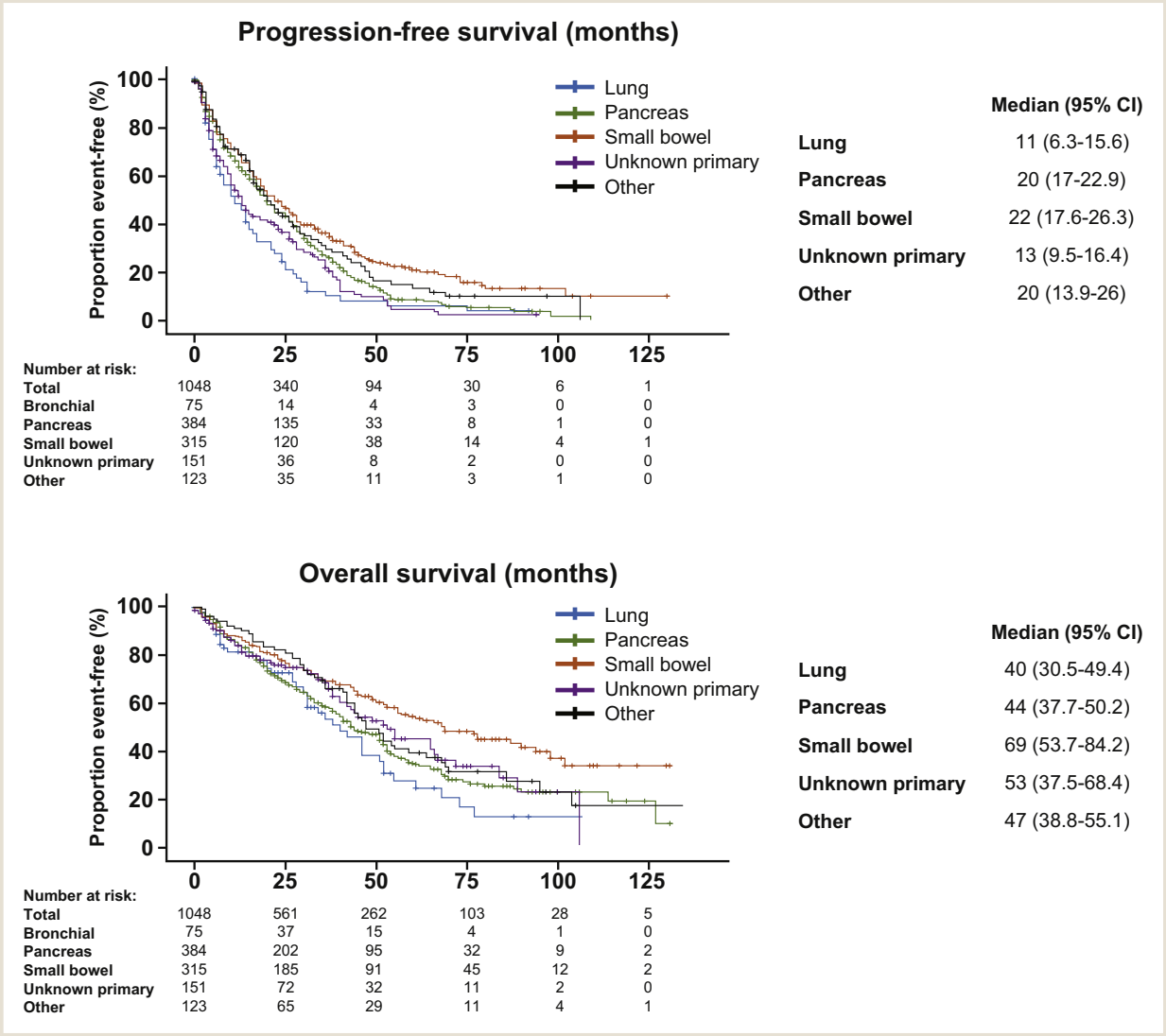
Peptide receptor radionuclide therapy safety outcomes appear to be consistent among the 5 studies that exclusively focused on patients with lung typical/atypical carcinoids (Table 5).[42,55-58] The entire patient population received PRRT with ^{177}Lu-DOTATATE only in 3 of the 5 studies, and this agent appeared to be well tolerated by patients with lung typical/atypical carcinoids, with few reports of major hematologic or renal toxicities.[42,57,58] The retrospective analysis of 114 patients with lung typical/atypical carcinoids treated with ^{177}Lu-DOTATATE, ^{90}Y-DOTATOC, or both agents, provides the most comprehensive safety outcomes of the reviewed studies.[55] No MDS or acute leukemia was observed in these patients.[55] Previous use of chemotherapy was associated with an increased risk of developing reduced renal function.[55]

Table 3 Tumor Response and Survival in Studies Reporting Combined ^{177}Lu and ^{90}Y-PRRT Outcomes for Patients With Lung TC/AC

PRRT Agent	Type of Study	Reference	Total Patient Group	Relevant Patient Group With Treatment Outcome	Response Criteria	CR	PR	MR	SD	PD	ORR	DCR	PFS	OS
						n (%)							Median in Months	
^{90}Y-DOTATATE or ^{90}Y-DOTATOC in 56%, ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC in 15%, ^{90}Y and ^{177}Lu-PRRT in different cycles in 29%	Phase II	Filice et al[59]	Advanced NET with baseline PD and SSTR$^+$ imaging (n = 59)	Lung TC/AC (n = 13)	Nonstandard (similar to WHO)	0	8 (62)	NA	3 (23)	2 (15)	8 (62)	11 (85)	NS	NS
^{90}Y-DOTATATE or ^{90}Y-DOTATOC in 15%, ^{177}Lu-PRRT in 36%, ^{90}Y and ^{177}Lu-PRRT in different cycles or the same cycle in 49%	Retrospective	Baum et al[53]	NEN of all grades with baseline PD or disease symptoms and SSTR$^+$ imaging (n = 1048)	Bronchial NEN (n = 75)	RECIST version 1.1	NS	NS	NS	NS	NS	NS	NS	11 (95% CI, 6.3-15.6)	40 (95% CI, 30.5-49.4)
^{90}Y-PRRT in 83%, ^{177}Lu-PRRT in 15%	Retrospective	Sharma et al[67]	Metastatic NET (n = 135)	Lung TC/AC (n = 18)	Nonstandard	NS	NS	NS	NS	NS	NS	NS	TTP 18.6 (IQR 7.5-61.9)	32.4 (IQR 18.4 to >137.6)
^{177}Lu-DOTATATE in 42%, ^{90}Y-DOTATOC in 39%, both in 18%	Retrospective	Mariniello et al[55]	Advanced bronchopulmonary TC/AC and SSTR$^+$ imaging (n = 114); 78% with baseline PD	Total (n = 114)	RECIST with MR (▼ <30%)	0	15 (13)	15 (13)	46 (41)	38 (33)	30 (27)	76 (67)	28.0 (IQR 14.9-45.1)	58.8 (IQR 32-91.6)
				^{177}Lu (n = 48)		0	6 (13)	8 (17)	22 (46)	12 (25)	14 (29)	36 (75)	31.0 (IQR 21.0-49.1)	NR
				^{90}Y (n = 45)		0	4 (9)	4 (9)	16 (36)	21 (47)	8 (18)	24 (55)	23.1 (IQR 12.0-39.1)	46.1 (IQR 22.9-69.0)
				^{177}Lu and ^{90}Y (n = 21)		0	5 (24)	3 (14)	8 (38)	5 (24)	8 (38)	16 (76)	31.1 (IQR 23.0-58.1)	61.0 (IQR 32.0-NR)
^{90}Y DOTATATE in 64%, ^{177}Lu-DOTATATE in 36%	Retrospective	Koffas et al[56]	Advanced bronchial TC/AC with baseline PD (n = 22)	Total (n = 22)	NS	NS	NS	NS	NS	NS	NS	NS	Mean TTP 14.1	Mean 26
^{90}Y-DOTATOC in 77%, ^{177}Lu-DOTATOC or both in 23%	Retrospective	Pfeifer et al[68]	Advanced NET with SRS$^+$ (n = 69); baseline PD in 61%	Bronchopulmonary TC/AC (n = 6)	RECIST version 1.0	0	1 (17)	NA	3 (50)	2 (33)	1 (17)	4 (67)	NS	NS

Abbreviations: AC = atypical carcinoids; DCR = disease control rate (including CR, PR, minor response [if applicable], and SD); IQR = interquartile range; MR = minor response; NEN = neuroendocrine neoplasms; NET = neuroendocrine tumors; NR = not reached; NS = not stated; PFS = progression-free survival; PRRT = peptide receptor radionuclide therapy; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumors; SRS = somatostatin receptor scintigraphy; SSTR = somatostatin receptor; TC = typical carcinoids; TTP = time to tumor progression; WHO = World Health Organization.

Figure 2 Progression-Free Survival and Overall Survival After Peptide Receptor Radionuclide Therapy (PRRT) in Patients With Neuroendocrine Neoplasms (NEN) of All Grades



Abbreviation: CUP = carcinoma of unknown primary.

^{177}Lu-DOTATATE monotherapy was not significantly associated with any grade of hematologic or renal AE, whereas ^{90}Y-DOTA-TOC monotherapy was identified as a risk factor for development of nephrotoxicity ($P = .009$), regardless of previous chemotherapy, and was associated with anemia of any grade ($P = .049$).[55] The combination of Lutetium-177 and Yttrium-90 PRRT agents in this study was an independent risk factor for developing moderate to severe grade leukopenia ($P = .012$).[55]

Hormonal crises (worsening diarrhea, severe flushing) are infrequent AEs that occur after the first cycle of PRRT.[70] A single-institution retrospective analysis of 479 patients who received ^{177}Lu-DOTATATE between 2000 and 2007 showed that 2 of 6 patients with lung carcinoids experienced hormonal crises after the first PRRT administration and required hospitalization for 5 and 11 days, respectively.[70] Hormonal crises that occur with PRRT are expected to be exceptionally rare in patients with lung carcinoids because few patients have carcinoid syndrome.[71]

Future Use of PRRT for Lung Typical/Atypical Carcinoids

Sequencing of PRRT Among Other Therapies for Lung Typical/Atypical Carcinoids

Currently only 1 therapy is approved by the EMA and the FDA for the treatment of patients with advanced lung typical/

Table 4 Symptom Control in PRRT Studies With an Exclusive Focus on Patients With Lung TC/AC

PRRT Agent	Type of Study	Reference	Patients	Patients With Symptoms From Functional Syndrome	Functional Syndrome Symptom Control
^{177}Lu-DOTATATE	Phase II	Ianniello et al[42]	Metastatic bronchial TC/AC with baseline PD and SRS^{+} (n = 34)	24% (8/34) had carcinoid syndrome	• Not stated
^{177}Lu-DOTATATE	Retrospective	Sabet et al[57]	Metastatic WD pulmonary TC/AC with SSTR^{+} imaging (n = 22); 77% with baseline PD	45% (10/22) had functional symptoms	• 30% (3/10) had complete and 70% (7/10) had partial resolution of functional symptoms
^{177}Lu-DOTATATE	Retrospective	Parghane et al[58]	Advanced pulmonary NEN with SSTR^{+} imaging (n = 22)	68% (15/22) had carcinoid syndrome	• Not stated specifically for carcinoid syndrome patients; however, among those who had tumor-related symptoms (all 22 patients), complete symptomatic improvement was achieved in 42% (8/19), partial symptomatic response in 26% (5/19), and SD in 11% (2/19) • 53% (10/19) had a biochemical improvement
^{177}Lu-DOTATATE in 42%, ^{90}Y-DOTATOC in 39%, both in 18%	Retrospective	Mariniello et al[55]	Advanced bronchopulmonary TC/AC and SSTR^{+} imaging (n = 114); 78% with baseline PD	32% (37/114) had carcinoid syndrome, and 4% (4/114) had Cushing syndrome	• Not stated, however, exacerbation of carcinoid syndrome in 2 patients was reported as an adverse event
^{90}Y DOTATATE in 64%, ^{177}Lu-DOTATATE in 36%	Retrospective	Koffas et al[56]	Advanced bronchial TC/AC with baseline PD (n = 22)	55% (12/22) had carcinoid syndrome or respiratory symptoms	• Not stated specifically for patients with carcinoid syndrome; however, symptomatic improvement occurred in 83% (10/12) who had carcinoid syndrome or respiratory symptoms • Biochemical improvement (>50% decrease in CgA) in 28%

Abbreviations: AC = atypical carcinoids; CgA = chromogranin A; NEN = neuroendocrine neoplasms; PRRT = peptide receptor radionuclide therapy; SRS = somatostatin receptor scintigraphy; SSTR = somatostatin receptor; TC = typical carcinoids; WD = well differentiated.

atypical carcinoids. Among other indications, including GEP NET, everolimus (Afinitor; Novartis Pharmaceutical Corporation, East Hanover, NJ) is approved for the treatment of adult patients with progressive, well differentiated, nonfunctional NET of lung origin with unresectable, locally advanced, or metastatic disease.[72,73] SSAs are not currently approved for patients with lung typical/atypical carcinoids, although according to the ENETS treatment guidelines, SSAs may be considered in the first-line treatment of advanced lung NET with low proliferative activity (ie, typical carcinoids) and strong SSTR expression on imaging, on the basis that low-grade lung NET are likely to have a clinical behavior similar to Grade 1 GEP NET.[74] The National Comprehensive Cancer Network treatment guidelines also recommend octreotide or lanreotide as first-line treatment options to consider in SSTR^{+} and/or functional lung typical/atypical carcinoids.[75] The efficacy and safety of long-acting lanreotide in lung typical/atypical carcinoids are currently being investigated in a phase III trial (SPINET [Efficacy and Safety of Lanreotide Autogel/ Depot 120 mg vs. Placebo in Subjects With Lung Neuroendocrine Tumors]; Clinicaltrials.gov identifier NCT02683941). Other first-line treatment options for lung typical/atypical carcinoids provided by the treatment guidelines include everolimus for typical and atypical carcinoids,[74,75] and chemotherapy for select patients with atypical carcinoids (cisplatin or carboplatin in combination with etoposide, or temozolomide).[75] PRRT is listed as a treatment option for patients with tumors that show strong expression of SSTR[9,74] and progression during treatment with SSAs.[75] Currently no data are available to guide sequencing of therapies in patients with advanced lung typical/atypical carcinoids. However, the potential of reduced renal function (Grade 1/2 serum creatinine increases) with PRRT after chemotherapy might be considered when sequencing therapies.[55] On the basis of our own clinical experience and the efficacy and toxicity data available for all possible treatments, experienced multidisciplinary teams should consider use of PRRT alongside everolimus as an option for advanced, patients with SSTR^{+} lung typical/atypical carcinoids with disease progression during treatment with SSAs.

Future Combination of PRRT With Other Therapies for Lung Typical/Atypical Carcinoids

Two clinical trials have reported treatment outcomes for patients with lung typical/atypical carcinoids who received PRRT in combination with chemotherapy. A phase II trial of 33 patients with well differentiated, progressing NET treated with ^{177}Lu-DOTATATE in combination with capecitabine reported 100% disease control for the only 2 patients with lung typical/atypical carcinoids included in the trial.[76] A phase I/II trial of 35 patients with low-grade, progressing NET treated with ^{177}Lu-DOTATATE in combination with capecitabine and temozolomide reported stable disease and a PD for the 2 patients with lung typical/atypical carcinoids.[77] More clinical trials will likely be needed to investigate efficacy of PRRT in combination with other systemic treatments, including use of cytotoxic and immunostimulatory agents, in patients with lung typical/atypical carcinoids. Clinical trials are also needed to determine whether SSAs should be continued in patients with disease progression

Table 5 Safety in PRRT Studies With an Exclusive Focus on Patients With Lung TC/AC

PRRT Agent	Type of Study	Reference	Patients	Toxicity Assessment Criteria	Reported Safety Results
^{177}Lu-DOTATATE	Phase II	Ianniello et al[42]	Metastatic bronchial TC/AC with baseline PD and SRS^{+} (n = 34)	CTCAE version 3.0	• No major acute or delayed toxicity (Grade 3 or 4) occurred in either group or with either therapeutic cumulative activity
^{177}Lu-DOTATATE	Retrospective	Sabet et al[57]	Metastatic WD pulmonary TC/AC with SSTR^{+} imaging (n = 22); 77% with baseline PD	CTCAE version 3.0	• No serious acute adverse events • Grade 3 hematotoxicity was observed 3-10 weeks after at least 1 of the administrations in 3 patients (13.6%) • Mean time to complete bone marrow recovery was 19 (range, 9-22) months after termination of PRRT • No Grade 3 or higher nephrotoxicity during follow-up • Mean relative change of GFR was −1% per year • No other relevant toxicities or treatment-related deaths
^{177}Lu-DOTATATE	Retrospective	Parghane et al[58]	Advanced pulmonary NEN with SSTR^{+} imaging (n = 22)	Not stated	• No major hematologic and renal toxicity in any patient, except for 2 patients who had Grade 1 renal and hematologic toxicity in the initial PRRT cycles and recovery in subsequent follow-up
^{177}Lu-DOTATATE in 42%, ^{90}Y-DOTATOC in 39%, both in 18%	Retrospective	Mariniello et al[55]	Advanced bronchopulmonary TC/AC and SSTR^{+} imaging (n = 114); 78% with baseline PD	CTCAE version 4.0	• Most hematologic and renal adverse events after PRRT were mild, and no severe (Grade 3/4) serum creatinine increases occurred • No myelodysplastic syndrome or acute myeloid leukemia were observed • Except for carcinoid syndrome exacerbation in 2 patients, no life-threatening consequences or deaths related to PRRT were observed • ^{177}Lu-DOTATATE monotherapy group: no patients had Grade 3 anemia, Grade 3 leukopenia, or Grade 3 thrombocytopenia • ^{90}Y-DOTATOC monotherapy group: 1 Grade 3 anemia, 2 Grade 3 leukopenia, and 2 Grade 3 thrombocytopenia • ^{177}Lu with ^{90}Y PRRT group: 1 Grade 3 anemia, 1 Grade 3 leukopenia, and no Grade 3 thrombocytopenia • ^{177}Lu-DOTATATE monotherapy was not significantly associated with any grade of hematologic or renal adverse event • ^{90}Y-DOTATOC monotherapy was identified as an independent risk factor for serum creatinine increase (OR, 3.32; 95% CI, 1.34-8.19, P = .009) and therefore development of nephrotoxicity, regardless of previous treatment with chemotherapy • ^{90}Y-DOTATOC monotherapy was also identified to have an association with anemia of any grade (P = .049) • The combination protocol was an independent risk factor for developing moderate to severe grade leukopenia (OR, 5.2; 95% CI, 1.44-18.6; P = .012), regardless of previous treatment with chemotherapy • Previous chemotherapy was associated with an increased risk of developing a decrease in renal function (OR, 2.92; 95% CI, 1.24-5.90)
^{90}Y DOTATATE in 64%, ^{177}Lu-DOTATATE in 36%	Retrospective	Koffas et al[56]	Advanced bronchial TC/AC with baseline PD (n = 22)	WHO	• Bone marrow toxicity: Grade 1 in 3 patients, Grade 2 in 2 patients, Grade 3 in 1 patient • Renal toxicity: none

Abbreviations: AC = atypical carcinoids; CTCAE = Common Terminology Criteria for Adverse Events; GFR = glomerular filtration rate; NEN = neuroendocrine neoplasms; NET = neuroendocrine tumors; PRRT = peptide receptor radionuclide therapy; SCLC = small-cell lung carcinoma; SRS = somatostatin receptor scintigraphy; SSTR = somatostatin receptor; TC = typical carcinoids; WD = well-differentiated; WHO = World Health Organization.

during treatment with SSAs and who subsequently receive PRRT. The role of continuing SSAs beyond PRRT, although frequently done, still needs to be clarified. A recent retrospective study of patients with Grade 1/2 metastatic GEP NET suggested a substantial benefit in PFS and OS when SSAs were continued beyond PRRT.[78] Ideally these findings should be verified in a randomized trial including patients with lung typical/atypical carcinoids.

Future PRRT Agents for Lung Typical/Atypical Carcinoids

One patient with a lung typical/atypical carcinoid was included in a small (n = 4) pilot study of a novel PRRT agent, ^{177}Lu-DOTA-JR11 (also known as ^{177}Lu-OPS201), which has a high affinity for SSTR2 and acts as an antagonist.[79] The patient experienced a PR at 3- and 12-month follow-ups. AEs reported included Grade 1 anemia and leukopenia and Grade 3 thrombocytopenia, which were reversible.[79] Two clinical trials of PRRT in NET are ongoing and include patients with lung typical/atypical carcinoids; these trials both involve the SSTR antagonist ^{177}Lu-OPS201. A phase I/II trial, with an estimated completion date of May 2022 is recruiting patients with NET to evaluate the safety and tolerability of ^{177}Lu-OPS201 (Clinicaltrials.gov identifier NCT02592707). Another trial is investigating the effectiveness of theranostics with ^{68}Ga-DOTA-JR11 and ^{177}Lu-OPS201 in patients with metastatic and/or unresectable well differentiated NET or panNET with PD (Clinicaltrials.gov identifier NCT02609737). The primary end point is ORR, and the expected completion date is November 2019.

Conclusion

Overall, efficacy data (especially DCR) from clinical studies of PRRT in patients with advanced lung typical/atypical carcinoids is comparable with the results of NETTER-1, regardless of which PRRT agent(s) were used for treatment. This might reflect a universal mechanism of PRRT action on any SSTR-expressing NET. However, some studies might indicate that the underlying biology of individual tumors likely plays a role in their response to PRRT, because patients with atypical carcinoids had a lesser chance of having their disease controlled with this treatment modality. Whether this phenomenon is simply related to a presumably lower rate of SSTR expression in atypical carcinoids, or other relevant biological differences, remains to be studied. Keeping in mind the limitations related to the retrospective nature of most of the available studies, PRRT in patients with lung typical/atypical carcinoids showed a side effect profile that is not significantly different from that seen in the NETTER-1 trial and other large studies of GEP NET. On the basis of the available data, experienced multidisciplinary teams might consider PRRT alongside everolimus and other treatment choices as an off-label option for patients with advanced, SSTR$^+$ lung typical/atypical carcinoids that are progressing during treatment with SSAs.

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Supplemental Data

Supplemental Appendix 1

Peptide Receptor Radionuclide Therapy Procedure Summary at the Mayo Clinic

Patient Selection. When the PRRT order or preauthorization is received by the Mayo Clinic's Nuclear Medicine Therapy core team, patients are screened by a nuclear radiologist or nuclear medicine physician to assess eligibility for PRRT. The type and grade of NET, pathology results, liver tumor burden, and signs of disease progression are key indicators for appropriateness of therapy. Somatostatin receptor imaging, either with Gallium-68 DOTATATE or Octreoscan, should be available, preferably performed within the past 6 months. Additional imaging with computed tomography and/or magnetic resonance imaging are also reviewed, if available, to assess the extent of disease (sites involved) as well as signs of disease progression. The most recent laboratory tests are also reviewed, including hepatic function, renal function, and complete blood count. If the patient is considered suitable for PRRT, the physician communicates with the lead nuclear medicine therapy technologist to schedule the patient for therapy. Patients are also discussed at the biweekly tumor board. A note regarding the final decision from the NET tumor board meeting is provided in the patient's chart by either the nuclear medicine physician or nuclear radiologist.

Patient Preparation. Suspend treatment with long-acting octreotide for 1 month and short-acting octreotide for 24 hours before PRRT initiation.

Repeat laboratory tests in the 48 hours before therapy (usually patients will have a medical oncology visit the day before the therapy).

Patient Status.

- Any history of previous external beam radiation, if it involved more than 25% of bone marrow; therapy not recommended
- Interferon, everolimus, or other systemic therapies within past 5 days; therapy not recommended
- Systemic chemotherapy (particularly temozolomide) should be discontinued for 4 weeks

The Day of Therapy. The length of stay for therapy is usually 6 to 8 hours. This therapy can be performed in an outpatient setting or at an infusion clinic, depending on availability. The room in which therapy will be provided needs to be prepared by a nuclear medicine team for potential radioactive spills or contamination.

Patients are requested to check in during the early morning. The first visit will be from the nuclear medicine team. The nuclear medicine physician or nuclear radiologist will obtain consent, sign written directive, and explain radiation safety guidelines. Radiation safety guidelines mostly focus on possible contamination by bodily fluids (especially urine) and contact precautions. Short-term and long-term possible side effects need to be discussed with the patient before proceeding with therapy. Written guidelines should be provided, including those for radiation safety.

After the I.V. team visit, the patient receives premedication with an antiemetic. After premedication, administration of the amino acid solution is initiated and is typically continued for 4 hours. Thirty minutes after the start of amino acid solution administration, Lutetium is administered for approximately 1 hour. If all goes well, the patient will be discharged approximately 30 minutes after completion of the amino acid infusion. Patients should be cleared for discharge by a radiation safety officer.

Nursing support during therapy is critical, because patients might need immediate assistance to manage side effects. Nurses, pharmacy, radiation safety, the nuclear medicine therapy team, and a referring oncology team work closely together during treatment administration. The nuclear medicine team monitors patients closely to make sure radioactive therapy infusion is administered on time and without evidence of extravasation or contamination.

Patients do not fast before or during therapy; instead they are advised to eat well if they can, to avoid hypoglycemia. Patients should stay well-hydrated during and after therapy. Institutional guidelines should be developed and followed for possible PRRT side effects, including exacerbation of hormonal symptoms such as hypoglycemia, nausea, vomiting, and, in rare circumstances, carcinoid crisis.

Supplemental Appendix 2

Lutathera (Advanced Accelerator Applications USA, Inc) Administration According to Pump Protocol at the Banner M.D. Anderson Cancer Center

Tools Needed.

1) Curlin therapy pump by MOOG
2) Male to male adaptor
3) Three-way stop-cock
4) Infusion administration set by MOOG (3.4 mL tubing for pump)
5) 18-gauge, 3.5-inch spinal needle
6) Micron filter
7) 18-gauge, 1.5-inch vent needle
8) Forceps
9) Gloves
10) L-block placed on a moveable cart (to accommodate patient positioning)
11) 10-cc saline syringe or 10-cc vial of sterile water (to prime tubing)

Pump Set-up.

1) Twist yellow tab off of tubing clamp
2) Attach male to male adaptor on side of tubing closest to yellow clamp
3) Attach spinal needle to other end of male to male adapter
   a. Lift metal lever on top of pump
   b. Place blue pin in right side of pump
   c. Place yellow pin in left side of pump
   d. Close lever and secure

Pump Programming for Lutathera (Advanced Accelerator Applications USA, Inc) Therapy Infusion.

1) Turn pump on (orange top left button)
2) Highlight "Program" then hit "YES" button
3) Arrow down to new program then hit "YES" button
4) Highlight "Continuous" then hit "YES" button
5) Hit "YES" to erase RX
6) "Continuous" should be displayed on the left-hand side and "unidentified" should be displayed at the top
7) Hit "YES" to all (units [mL], delay [OFF], medLMTS [OFF], next [YES])
8) Enter bag volume 24.9, hit "YES" button
9) Volume to be administered 23 mL. Hit "YES" button
10) Arrow passed rate
11) Set time for 25 minutes (rate will now be 55.2 mL per hour).
12) KVORATE will always be 0.1 mL per hour
13) Done "YES"

PRIME TUBING

14) Place spinal needle in 10-cc syringe saline or 10-cc vial of sterile water
15) Hit prime tubing button (bottom right green button). Hold prime tubing button until all of tubing is primed

Turn pump off until use (program will be saved)

Vent Dose Before Patient Setup.

1) Attach 3-way stop-cock (male side to micron filter) with the "off" switch facing left
2) Attach micron filter to 18-gauge vent needle
3) Spike dose at angle in the outer portion of rubber septum. Ensure needle is air pocket

Connect Pump to Dose.

1) Spike dose with spinal needle at angle in the outer portion of rubber septum. Ensure needle is at the bottom of vial
2) Attach other end of primed pump tubing to patient
3) Hit "ON" switch on pump
4) Enter to select program
5) Repeat RX-Yes
6) System will run through the previously set-up program. When done, hit "RUN TO START"

Infusion is 25 minutes
Infusion complete will be displayed

Flush Vial.

1) Hit "PAUSE" button
2) Attach 10-mL syringe of saline to top of 3-way stop-cock
3) Infuse 5 mL saline into top of 3-way stop-cock (keep saline syringe attached for the remaining duration of the infusion)
4) Hit "REPEAT RX" and change amount to be administered to 5 mL
5) Change time to 3 minutes
6) Swirl vial with forceps to mix up remaining Lutathera (Advanced Accelerator Applications USA, Inc) with saline
7) Hit "Run"

When infusion complete

8) Add remaining 5 mL saline to top of 3-way stop-cock
9) Hit "REPEAT RX" and change amount to be administered to 8 mL (to flush remaining fluid in line along with the 5 mL saline just injected into vial)
10) Hit "Run" (infusion complete when air in line error occurs)

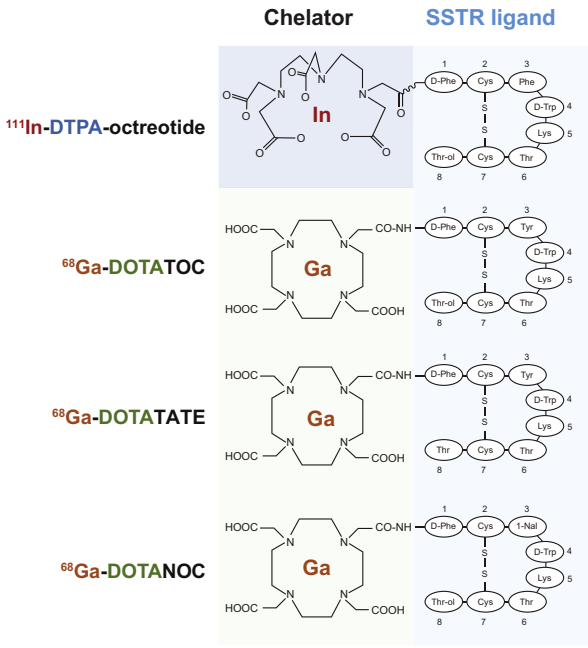
Turn off pump when complete

** Dispose of all tools in Mayo jar and store until background**

The patient is then scanned from top of head to thigh approximately 2 to 3 hours after the Lutathera (Advanced Accelerator Applications USA, Inc) infusion. The patient is released when amino acids are complete and patient's exposure rate is measured below 2 milliroentgen per hour. The total time from start to finish is generally 6 to 8 hours. The patient's room is monitored, and unless accidents have occurred (ie, urine or blood contamination) the patient's room is at background and released.

One bathroom is designated for our Lutathera (Advanced Accelerator Applications USA, Inc) patients for the day, and it is monitored and released when the toilet exposure rate is less than 4 milliroentgen per hour at 1 m.

Supplemental Figure 1 Chemical Structure and Binding Affinity (Half-Maximal Inhibitory Concentration in nM; Mean ± Standard Error) of SSTR Imaging Agents. Data from NETSPOT package insert[13]



	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
^{111}In-DTPA-octreotide	>10,000	22 ± 3.6	182 ± 13	>1000	237 ± 52
^{68}Ga-DOTATOC	>10,000	2.5 ± 0.5	613 ± 140	>1000	73 ± 21
^{68}Ga-DOTATATE	>10,000	0.20 ± 0.04	>1000	300 ± 140	377 ± 18
^{68}Ga-DOTANOC	>10,000	1.9 ± 0.4	40.0 ± 5.8	260 ± 74	7.2 ± 1.6

Abbreviation: SSTR = somatostatin receptor.
Adapted with permission from Fani et al. Somatostatin receptor antagonists for imaging and therapy. J Nucl Med 2017; 58:61s-6s.

Supplemental Figure 2 Tumor Detection Rate of Gallium-68 DOTATATE, DOTATOC, or DOTANOC Positron Emission Tomography Imaging in Patients With Lung Typical/Atypical Carcinoids. Data from Kayani et al,[32] Pericleous et al,[33] Kumar et al,[34] Jindal et al,[35] Venkitaraman et al,[10] Prasad et al,[36] Ambrosini et al,[37] Lamarca et al,[38] and Lococo et al[39]