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Expanding the therapeutic horizon of ^{177}Lu-DOTATATE: a review of current evidence

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ABSTRACT

Neuroendocrine tumors (NETs) are a heterogenous group of neoplasms originating from neuroendocrine cells, most frequently found in the gastrointestinal tract and pancreas. A defining feature of NETs is the overexpression of somatostatin receptors (SSTRs), particularly subtype 2 (SSTR2), which is the primary target for both diagnostic imaging and therapeutic interventions. Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE, a radiolabeled somatostatin analog, has emerged as a transformative alternative for patients with advanced or progressive well-differentiated NETs. Considering that SSTR expression is also present in various other tumors—including pheochromocytomas, paragangliomas, meningiomas, and medullary thyroid carcinomas—there is increasing interest in expanding the use of PRRT to other SSTR-positive malignancies. This review aimed to present evidence, explore ongoing clinical research, and highlight emerging directions for ^{177}Lu-DOTATATE therapy beyond gastroenteropancreatic NETs.

Keywords: neuroendocrine tumors (NETs), somatostatin receptors (SSTRs), peptide receptor radionuclide therapy (PRRT), ^{177}Lu-DOTATATE, gastroenteropancreatic NETs (GEP-NETs)

Abbreviations:
^{131}I-MIBG: [^{131}I]-meta-iodobenzylguanidine
AD: absorbed dose
BC: bronchial carcinoid
CR: complete response
DCR: disease control rate
DTC: differentiated thyroid cancer
GEP: gastroenteropancreatic
MTC: medullary thyroid cancer
NETs: neuroendocrine tumors
ORR: objective response rate
OS: overall survival
PD: progressive disease
PET/CT: positron emission tomography/computed tomography

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PFS: progression-free survival
PPGLs: pheochromocytomas and paragangliomas
PR: partial response
PRRT: peptide receptor radionuclide therapy
RAI: radioactive iodine
SD: stable disease
SPECT: single photon emission computed tomography
SSTRs: somatostatin receptors
TC: thyroid cancer
WHO: World Health Organization

INTRODUCTION

Neuroendocrine tumors (NETs) are a group neoplasms originating from neuroendocrine cells, with the gastrointestinal tract and pancreas being the most commonly affected sites.[1] These tumors typically exhibit slow-growing clinical behavior, variable hormonal activity, and overexpression of somatostatin receptors (SSTRs), particularly somatostatin receptor 2 (SSTR2), on the tumor cell surface.[2] The overexpression of SSTRs forms the molecular basis for SSTR-targeted imaging and therapy, offering effective diagnostic and therapeutic strategies for managing NETs.

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE, a radiolabeled somatostatin analog, has emerged as an important therapeutic approach for patients with advanced, unresectable, or progressive well-differentiated NETs (Fig. 1).[3] The pivotal NETTER-1 trial demonstrated that ^{177}Lu-DOTATATE plus intramuscular octreotide long-acting repeatable (LAR) (30 mg) significantly improved progression-free survival (PFS) and objective response rate

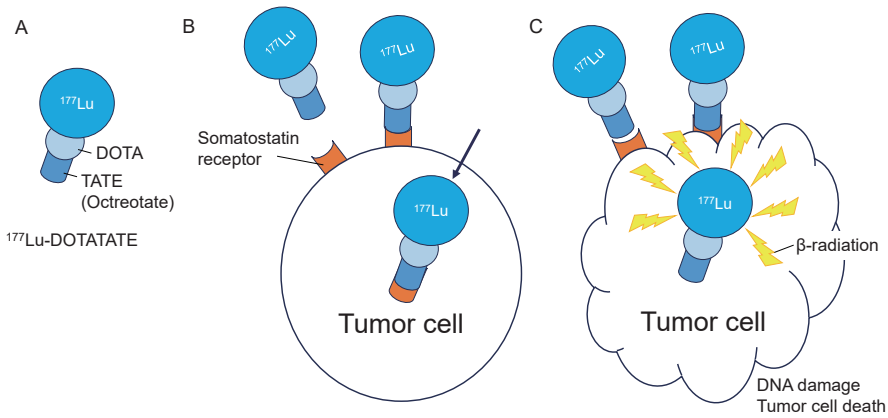

Fig. 1 Therapeutic mechanism of ^{177}Lu-DOTATATE in SSTR-positive tumors

Fig. 1A: ^{177}Lu-DOTATATE is a radiopharmaceutical agent composed of the somatostatin analog Tyr^3-octreotate labeled with the β-emitting radionuclide ^{177}Lu via the chelating agent DOTA.

Fig. 1B: Following administration, it primarily binds to the SSTR (mainly type 2) and is internalized into tumor cells.

Fig. 1C: The emitted beta-particles induce DNA damage, thereby inhibiting tumor cell proliferation. The maximum β energy of ^{177}Lu is 498 keV, with a maximum tissue penetration of approximately 2.2 mm, enabling effective tumor irradiation while minimizing damage to adjacent normal tissues.

SSTR: somatostatin receptor

(ORR) compared with high-dose octreotide LAR in patients with midgut NETs.[4] These findings established the efficacy and safety of PRRT, positioning it as a key option in the therapeutic algorithm for NETs. Following the NETTER-2 trial, first-line ^{177}Lu-DOTATATE plus octreotide LAR significantly extended the median PFS by 14 months in patients with grade 2 or 3 advanced gastroenteropancreatic NETs (GEP-NETs).[5]

In addition to GEP-NETs, SSTRs are expressed in various other tumor types, including pheochromocytomas, paragangliomas, meningiomas, medullary thyroid carcinomas, and certain bronchial and thymic NETs. This wide distribution of SSTR expression has parked growing interest in expanding PRRT indications to these additional SSTR-positive malignancies.

This review aims to synthesize current evidence, explore ongoing clinical studies, and outline emerging directions for the use of ^{177}Lu-DOTATATE beyond the GEP setting.

MATERIALS AND METHODS

A comprehensive literature review was performed on PubMed up to February 27, 2025, to identify studies that reported the applications of ^{177}Lu-DOTATATE in human subjects. Studies focused exclusively on GEP-NETs, experimental (non-human) studies, and publications not available in English were excluded. Furthermore, ongoing clinical trials were identified through a search of ClinicalTrials.gov (accessed on April 1 and 2, 2025) using the keyword "177Lu-DOTATATE." Relevant references cited within the initially retrieved PubMed articles were also reviewed and included, where appropriate.

Thyroid cancer

Thyroid cancer (TC) is the most prevalent endocrine malignancy, with its incidence rising markedly in recent decades.[6,7] Differentiated TC (DTC), which encompasses papillary thyroid carcinoma, follicular thyroid carcinoma, and Hürthle cell thyroid carcinoma, is the most common subtype, accounting for approximately 90% of all TC cases. Medullary TC (MTC), arising from parafollicular (C) cells of the thyroid gland, represents approximately 5% of all TCs globally. Despite its relatively low incidence, MTC contributes to approximately 8% of TC-related deaths, highlighting its more aggressive clinical behavior.[8] The standard treatment for most patients with DTC includes thyroidectomy followed by radioactive iodine (RAI) therapy. This approach yields favorable outcomes, with a 10-year overall survival (OS) rate exceeding 90% in patients with localized disease. However, recurrence occurs in approximately 15% of patients, and approximately 10% develop distant metastases.[9]

RAI remains a cornerstone in the management of recurrent disease. However, patients with RAI-refractory DTC tend to exhibit a more aggressive clinical course, with a 5-year disease-specific survival rate ranging from 60% to 70% and a 10-year survival rate of approximately 10%.[10-12] For such cases, multi-kinase inhibitors, such as lenvatinib and sorafenib, have been established as standard treatments. Furthermore, patients with tumors harboring specific driver gene alterations—such as RET fusions and BRAF mutations—may benefit from targeted molecular therapies, which have demonstrated significant clinical efficacy.[13]

In contrast, MTC is inherently insensitive to RAI, and its overall prognosis is comparatively poorer. The 10-year OS rate for MTC ranges from 75% to 88%. Despite aggressive surgical management, nearly half of patients with MTC experience persistent or recurrent disease, which negatively impacts quality of life and reduces the 10-year survival rate by approximately 40%. In such cases, additional interventions—such as reoperation, embolization, or radiotherapy—may be necessary to improve clinical outcomes.[14,15]

Regarding SSTR expression, normal thyroid tissue lacks SSTR2a and SSTR2b but expresses SSTR1, SSTR3, SSTR4, and SSTR5. SSTR2b is commonly expressed in benign thyroid conditions, such as multinodular goiters and follicular adenomas. SSTR5 and SSTR2b are frequently expressed in DTC, suggesting their potential use as targets for somatostatin analog therapies. In contrast, SSTR expression in Hürthle cell adenomas is more variable.[16] MTC shows variable expression of SSTR subtypes.[17] Among these, SSTR2 is the most frequently expressed receptor, detected in 38% of cases, followed by SSTR5 and SSTR4.[18] Similar to MTC, patients with positive SSTR2a expression show significantly improved outcomes, with a longer 10-year OS than negative cases (10-year survival rate, 96% and 43%, respectively).[19]

Based on this biological background, ^{68}Ga-DOTATATE positron emission tomography/computed tomography (PET/CT) has emerged as a useful imaging modality for detecting TC.[20] In MTC, ^{68}Ga-DOTATATE PET/CT exhibited an overall sensitivity of 88.1% for detecting recurrent or metastatic disease, with particularly high accuracy in detecting bone metastases.[21,22] Although ^{68}Ga-DOTATATE PET/CT is a useful diagnostic modality for evaluating RAI-refractory DTC, its use may be best considered as a complementary tool due to the variable imaging characteristics of individual lesions.[23]

The expression profile for SSTR subtypes in TCs can help guide the selection of appropriate somatostatin-analog-based treatments. For PRRT in DTC and MTC, ^{90}Y-DOTATATE is among the most commonly used agents, followed by ^{177}Lu-DOTATATE and ^{111}In-octreotide.[24,25]

For ^{177}Lu-DOTATATE therapy, the administered activity typically ranges from 5.5 to 7.7 GBq per cycle, usually delivered over four cycles. However, the number of patients with recurrent TC treated with ^{177}Lu-DOTATATE in published studies remains limited (n = 1–8), and treatment protocols have often varied, particularly in terms of dosage and continuation across studies.[24] Regarding the safety profile of ^{177}Lu-DOTATATE, mild and transient hematological and renal toxicities (grade 1–2) have been reported, indicating a generally favorable tolerability.[24]

A systematic review reported that among 25 patients with advanced RAI-refractory DTC assessed for biochemical response after ^{177}Lu-DOTATATE, nine exhibited partial response (PR) and 11 demonstrated progressive disease (PD). In terms of radiographic outcomes, 19 patients exhibited an overall response rate of 11% (PR, 2; stable disease [SD], 8; PD, 9).[24]

In a study that investigated the efficacy of ^{177}Lu-DOTATATE in patients with de-differentiated thyroid carcinoma, which is characterized by elevated thyroglobulin levels and negative iodine scintigraphy, most tumors exhibited low-grade uptake on SSTR-based imaging (Grade II on a semiquantitative scale). In contrast, these lesions exhibited high uptake on ^{18}F-fluorodeoxyglucose (FDG)-PET imaging, suggesting a more aggressive tumor phenotype.[26]

Based on these observations, the authors concluded that ^{177}Lu-DOTATATE provides only modest therapeutic benefit in patients with SSTR-positive metastatic TC, particularly in those with aggressive disease biology. Among 74 patients with metastatic MTC treated with ^{177}Lu-DOTATATE, biochemical response evaluation revealed complete response (CR) in 5 patients, PR in 26 patients, SD in 14 patients, and PD in 29 patients. Radiographic response evaluation in 85 patients revealed PR in 9 patients, SD in 50 patients, and PD in 26 patients.[24] The overall response rate was 11%. Treatment of recurrent or metastatic TC with ^{177}Lu-DOTATATE has shown limited efficacy, and studies have reported high variability in treatment protocols and patient numbers. Table 1 presents the key findings.

Table 1 Summary of clinical, imaging, and therapeutic features of DTC and MTC

	DTC	MTC
Incidence	~90% of all thyroid cancers	~5% of all thyroid cancers
Sensitivity to RAI	High initially, but becomes refractory in ~10%	None
Recurrence or metastasis	~15% recurrence, ~10% distant metastasis	~50% develop persistent or recurrent disease
10-year overall survival[9-12,14,15]	>90% (localized), ~10% (if RR)	75–88%, reduced by ~40% with recurrence
SSTR expression profile	SSTR2b, SSTR5	SSTR2 > SSTR5, SSTR4
Cumulative activity[24]	5.55–33.3 GBq	2.6–30.8 GBq
^{177}Lu-DOTATATE biochemical response[24]	RR-DTC (n = 20): PR 45%, PD 55%	Metastatic MTC (n = 74): CR 7%, PR 35%, SD 19%, PD 39%
^{177}Lu-DOTATATE radiographic response[24]	RR-DTC (n = 19): PR 11%, SD 42%, PD 47%	Metastatic MTC (n = 85): PR 11%, SD 59%, PD 31%
Safety	Mild and transient hematologic and renal toxicities (grade 1–2)	

DTC: differentiated thyroid cancer
MTC: medullary thyroid cancer
RAI: radioactive iodine
RR: RAI-refractory
SSTR: somatostatin receptors
PR: partial response
PD: progressive disease
CR: complete response
SD: stable disease

Meningioma

Meningiomas are among the most common primary central nervous system tumors, accounting for approximately 37.6% of all cases.[27,28] Most cases are benign, with 80%–81% classified as typical (World Health Organization [WHO] grade 1), 17%–18% as atypical (WHO grade 2), and approximately 1.7% as anaplastic (WHO grade 3).[27] Despite their generally benign nature, approximately 20% of meningiomas exhibit aggressive behavior, characterized by high recurrence rates even after surgical resection and radiotherapy.[29-31] Recurrence rates are particularly high in higher-grade tumors: approximately 50%–94% in grade 3 meningiomas, 29%–52% in grade 2 meningiomas, and 7%–25% in grade 1 meningiomas.[32]

The prognosis for aggressive meningiomas remains poor. The reported 6-month PFS rates are approximately 29% for WHO grade 1 meningiomas and 26% for WHO grade 2 and 3 meningiomas.[33]

SSTR2 is overexpressed in 79%–100% of meningiomas, irrespective of the WHO grade.[34,35] This overexpression enables high-contrast imaging using ^{68}Ga-DOTATATE PET/CT, which has shown greater sensitivity than MRI for detecting meningiomas.[36,37] Considering its consistent expression, SSTR2 has also emerged as a promising therapeutic target, and several clinical studies

have explored PRRT for treating meningiomas.

Mirian et al conducted a meta-analysis of studies evaluating SSRT in patients with treatment-refractory meningiomas, encompassing publications from 1998 to 2015. The analysis included therapies using ^{90}Y-DOTATOC, ^{177}Lu-DOTATOC, ^{177}Lu-DOTATATE, or their combinations, with administered activities averaging 12,950 MBq (range, 1,688–29,772 MBq). The most frequently reported adverse events were grade 1 or 2 transient hematological toxicities, including anemia (22%), leukopenia (13%), lymphocytopenia (24%), and thrombocytopenia (17%). In total, 111 patients were included, classified as WHO grade I (33%), grade II (26%), grade III (17%), and unknown grade (23%). Patients received a median of three treatment cycles (range, 1–6 cycles) of SSRT. Although PR was achieved in only 2% of cases, SD was observed 58% and PD in 41%. PFS analysis based on 76 patients demonstrated 6-month and 12-month PFS rates of 61% and 53%, respectively. When stratified according to WHO grade, the 6-month PFS was 94% for grade I meningiomas, 48% for grade II meningiomas, and 0% for grade III meningiomas. OS at 6 and 12 months was 89% and 78%, respectively, with 12-month rates of 88% for grade I, 71% for grade II, and 52% for grade III tumors.[38]

In a prospective study, 14 patients with progressive WHO grade I–III meningiomas demonstrating sufficient ^{68}Ga-DOTATATE uptake were treated with ^{177}Lu-DOTATATE. Patients received 7.4 GBq intravenously every 8 weeks, up to four cycles. The therapy was generally well tolerated, with no unexpected safety concerns reported. The median number of treatment cycles administered was 3 (range, 1–4), and 43% of patients completed all four cycles. The best treatment response was SD in 9 patients (64%), whereas 4 patients (29%) experienced progression at the first follow-up. In this cohort, the 12-month PFS rate was 43%, and the 12-month OS rate was 71%. The median PFS and OS were 8.2 and 21.9 months, respectively.[39]

Another cohort study that involved 37 patients with progressive meningioma treated with ^{177}Lu-DOTATATE at 3.7 or 5.5 GBq per cycle reported that 62% of patients completed at least four cycles. The treatment was well tolerated, with no symptomatic toxicity observed. With a median follow-up of 46.7 months, the disease control rate (DCR) was 54%. The median PFS and OS were 15 months and 33 months, respectively.[40]

A Dutch study evaluated intra-arterial ^{177}Lu-DOTATATE PRRT in 13 patients with advanced meningioma who received a median of four cycles (range, 1–4 cycles) of ^{177}Lu-HA-DOTATATE at a mean activity of 7,428 ± 237 MBq per cycle (range, 6,000–7,700 MBq). Treatment was well tolerated, with mainly grade 1–2 hematological toxicities reported. The median overall PFS was 18 months, with stratified outcomes of 24 months for grade I, 4 months for grade II, and 18 months for tumors of unknown grade. The 6-month overall PFS rate was 76.9%, with rates of 100% for grade I, 25% for grade II, and 100% for unknown grade tumors.[41]

Seven studies, comprising 46 patients and 108 treatment cycles, reported on the tumor absorbed dose (AD) during ^{177}Lu-based SSRT. Substantial heterogeneity was observed in the imaging protocols and dosimetric calculations. The tumor AD ranged from 0.1 to 1.5 Gy/GBq in most cases, which was significantly lower than the values typically observed in NETs (1.3–22.9 Gy/GBq). Overall, the AD delivered to meningiomas with ^{177}Lu-based PRRT appeared relatively low, which may limit the therapeutic efficacy in certain cases.[42] Table 2 present the key findings.

Table 2 Summary of clinical studies on PRRT for meningiomas

Incidence	WHO grade I 80–81%, grade II 17–18%, grade III 1.7%
10-year overall survival	WHO grade I 88%, grade II 71%, grade III 52%
SSTR expression profile	SSTR2 is overexpressed in 79–100% of meningiomas, irrespective of WHO grade
Treatment demography	^{90}Y-/^{177}Lu-DOTATOC/DOTATATE (mean 12,950 MBq) mean 3 cycles (range, 1–6) (meta-analysis)[38] ^{177}Lu-DOTATATE, 7.4 GBq every 8 weeks, mean 3 cycles (range, 1–4) (prospective study)[39] ^{177}Lu-DOTATATE, 3.7–5.5 GBq/cycle (cohort study)[40]
Treatment response	PR, 2%; SD, 58%; PD, 41%[38] SD, 64%; PD, 29%[39] DCR, 54%[40]
Progression free survival	Progression free survival –6 months, 61% (by grade I, – 94%; II, – 48%; III, – 0%)[38] 8.2 months (median)[39] 15 months (median)[40]
Overall survival	Overall survival –12 months: 8% (by grade: I – 88%, II – 71%, III – 52%[38] 21.9 months (median)[39] 33 months (median)[40]
Safety profile	Mostly grade 1–2 hematologic toxicities, well tolerated[38] Generally mild, similar profile to grade I[39] Well tolerated, no unexpected adverse events[40]

PRRT: peptide receptor radionuclide therapy
SSTR: somatostatin receptors
PR: partial response
PD: progressive disease
SD: stable disease
WHO: World Health Organization
DCR: disease control rate

Bronchial carcinoid

Bronchial carcinoid (BC) tumors account for approximately 20%–30% of all NETs and represent approximately 1%–2% of all lung cancers.[43,44] These tumors, which include typical and atypical carcinoids, are more well-differentiated and less aggressive than other lung cancers, often leading to more favorable survival outcomes. Other studies have reported 5- and 10-year survival rates of 87% and 87%, respectively, for typical carcinoids and of 56% and 37%, respectively, for atypical carcinoids.[45] Data from a National Cancer Database analysis support these findings, showing similar 5-year survival rates of 92% for typical carcinoids and 85% for atypical carcinoids.[46]

BC tumors expression various SSTR subtypes, with SSTR1 detected in 52% of cases, SSTR2 in 75%, SSTR3 in 56%, SSTR4 in 16%, and SSTR5 in 32%. Expression patterns have prognostic

implications: negative SSTR2 and positive SSTR4 expression has been linked to lymph node involvement and distant metastasis. Furthermore, SSTR3 and SSTR4 expression correlate with shorter survival, whereas SSTR1 and SSTR2 expression is associated with improved clinical outcomes.[47] Considering its high prevalence and association with favorable prognosis, SSTR2 has emerged as a promising therapeutic target, prompting several clinical studies investigating PRRT for the treatment of BC tumors.

A prospective phase II trial evaluated the therapeutic effect of ^{177}Lu-DOTATATE in 34 patients with metastatic BC tumors. The median cumulative activity administered was 21.5 GBq (range, 12.9–27.8 GBq), and the interval between cycles was 6–8 weeks. In patients with typical carcinoids, the DCR was 80%, with CR observed in 6%, PR in 27%, and SD in 47%. For patients with atypical carcinoids, the DCR was 47%, with all patients achieving SD. The median PFS was 20.1 months for typical carcinoids and 15.7 months for atypical carcinoids. The median OS was 48.6 months for typical carcinoids and 37 months for atypical carcinoids. No major acute or delayed toxicities were observed, regardless of the cumulative activity. The study also noted that patients with thyroid transcription factor 1 (TTF-1) positivity had a significantly shorter median PFS (7.2 months) than TTF-1-negative cases (26.3 months).[48]

Brabander et al reported the efficacy of PRRT in 23 patients with BC tumors, among whom the response rates were 30% with PR, 30% with SD, and 26% with PD. At a median follow-up of 78 months, the median PFS was 20 months, and the median OS was 52 months.[48] In ^{177}Lu-DOTATATE therapy, a shorter OS has been reported in BC tumors (median OS, 52 months) than in midgut (median OS, 60 months) and pancreatic (median OS, 71 months) NETs.[49]

A meta-analysis that assessed the treatment response in 92 patients using RECIST 1.1 found a pooled disease response rate of 24% and a pooled disease control rate of 77%. PFS and OS were 21.6 and 48.8 months, respectively. Adverse effects were generally mild; however, rare but serious hematological toxicities occurred, including two cases of fatal acute myeloid leukemia. Nephrotoxicity, hepatotoxicity, and gastrointestinal symptoms were infrequent and mostly mild.[50]

In a related study evaluating the use of ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, or a combination of both for unresectable or metastatic BC tumors, the estimated median OS was 58.8 months, and the 5-year OS rate was 46.9%. The median PFS was 28.0 months, with a 5-year progression rate of 86.0%. When comparing the agents, ^{177}Lu-DOTATATE had a longer median PFS of 31.0 months and a lower 5-year progression rate of 81.4% than ^{90}Y-DOTATATE (23.4 months and 92.7%, respectively). Furthermore, ^{177}Lu-DOTATATE had better ORR and DCR than ^{90}Y-DOTATATE.[51] Mirvis et al reported that patients with bronchial NETs who were treated with ^{177}Lu-DOTATATE had a median PFS of 18 months, which is longer than the 12 months for those treated with ^{90}Y-DOTATATE, although the difference did not reach statistical significance.[52]

Furthermore, ^{177}Lu-DOTATATE was effective in alleviating the symptoms of carcinoid syndrome, including reductions in bowel movement frequency, flushing, and urinary 5-hydroxyindoleacetic acid excretion. Accordingly, it may be considered for symptomatic management when somatostatin analogs alone are insufficient.[53]

Parghane et al analyzed the response to PRRT for BC tumors in symptomatic, biochemical, and objective responses using molecular imaging and in objective response by anatomical imaging. The symptomatic response included 79% of the responders (CR, 42%; PR, 26%; SD, 11%; PD, 21%). The biochemical response included 53% of the responders (CR, 5%; PR, 16%; SD, 32%; PD, 47%). The objective response using molecular imaging included 53% of the responders (CR, 5%; PR, 11%; MR, 21%; SD, 16%; PD, 47%), and the objective response using anatomical imaging included 68% of the responders (CR, 5%; PR, 5%; MR, 21%; SD, 37%; PD, 32%).[54] PRRT has the advantage of symptomatic reduction and metabolic and volume reduction of lesions.

Zidan et al evaluated typical and atypical carcinoids using dual-tracer PET imaging with

^{18}F-FDG and ^{68}Ga-DOTATATE to assess their molecular imaging phenotypes. The study revealed substantial interpatient heterogeneity in both tracers, with approximately half of the patients exhibiting phenotypes considered unsuitable for PRRT.[55]

Among patients with high SSTR expression (modified Krenning score 3) on pretreatment ^{68}Ga-DOTATATE PET/CT, a median of four cycles (range, 1–4) of ^{177}Lu-DOTATATE was administered, with a median cumulative activity of 27 GBq (range, 6–43 GBq). The median PFS and OS were 23 and 59 months, respectively. Moderate concordance was observed between the response assessments by RECIST and ^{68}Ga-DOTATATE PET/CT. Among patients classified as having SD by RECIST, those who demonstrated PR on ^{68}Ga-DOTATATE PET/CT had longer OS than those without a metabolic response.[56]

Currently, recommendations for ^{177}Lu-DOTATATE in clinical guidelines suggest its use only after disease progression or intolerance to everolimus because of the higher level of evidence supporting the latter.[57,58] In the European Society for Medical Oncology (ESMO) clinical practice guidelines for lung and thymic carcinoids, PRRT is considered as a potential alternative third- or fourth-line therapy in patients in whom all RECIST-evaluable tumor deposits show a positive uptake on SSTR imaging after somatostatin analog and everolimus administration.[59]

^{177}Lu-DOTATATE has been well tolerated in patients with BC tumors. Several recent studies have investigated combination therapies involving ^{177}Lu-DOTATATE, including its use alongside immune checkpoint inhibitors such as nivolumab[60] and PARP inhibitors.[61]

The WHO guidelines emphasize a binary distinction between well-differentiated NETs encompassing typical and atypical carcinoids and poorly differentiated neuroendocrine carcinomas (NECs), including large-cell NEC (LCNEC) and small-cell lung carcinoma. Mitotic count and necrosis are the primary factors in this classification.[62] Another report demonstrated a remarkable response to ^{177}Lu-DOTATATE among patients with LCNEC with evident SSTR expression.[63] Table 3 presents the key studies, and Figure 2 presents a representative image of a BC tumor.

Table 3 Summary of clinical studies on ^{177}Lu-DOTATATE for BC tumors

Study	Subjects number	Cycles/cumulative activity	Response	PFS (months)	OS (months)	Toxicity	Notes
Ianniello et al,[48] 2016	34 (TC, 15; AC, 19)	4–5 cycles/median 21.5 GBq (12.9–27.8 GBq)	TC: CR, 6%; PR, 27%; SD, 47% AC: SD, 47%	TC, 20.1 AC, 15.7	TC, 48.6 AC, 37	No major toxicities	Phase II trial TTF-1 positivity associated with shorter PFS
Brabander et al,[49] 2017	23	Not specified	PR, 30%; SD, 30%; PD, 26%	20	52	–	Shorter OS than other NENs
Parghane et al,[54] 2017	22	4 cycles/median 20.1 (12.9–27.8GBq)	Symptomatic CR/PR/SD, 79% Biochemical CR/PR/SD, 53% Imaging CR/PR/MR/SD, 53%	–	40	–	Effective for symptomatic and metabolic response
Zidan et al,[56] 2022	48 (TC, 5; AC, 43)	Median 4 (range, 1–4) cycles/27GBq (range, 6–43)	40 patients with RECIST-measurable disease at 3 month PR, 20%; SD, 68%; PD, 12% DCR, 88%	23	59	Most grade 3/4 adverse events were reversible and the most common was lymphopenia (14%)	–

BC: bronchial carcinoid
TC: typical carcinoid
AC: atypical carcinoid
PFS: progression free survival
OS: overall survival
DCR: disease control rate
PR: partial response
PD: progressive disease
CR: complete response
SD: stable disease
MR: minor response
NENs: neuroendocrine neoplasms
TTF-1: thyroid transcription factor-1

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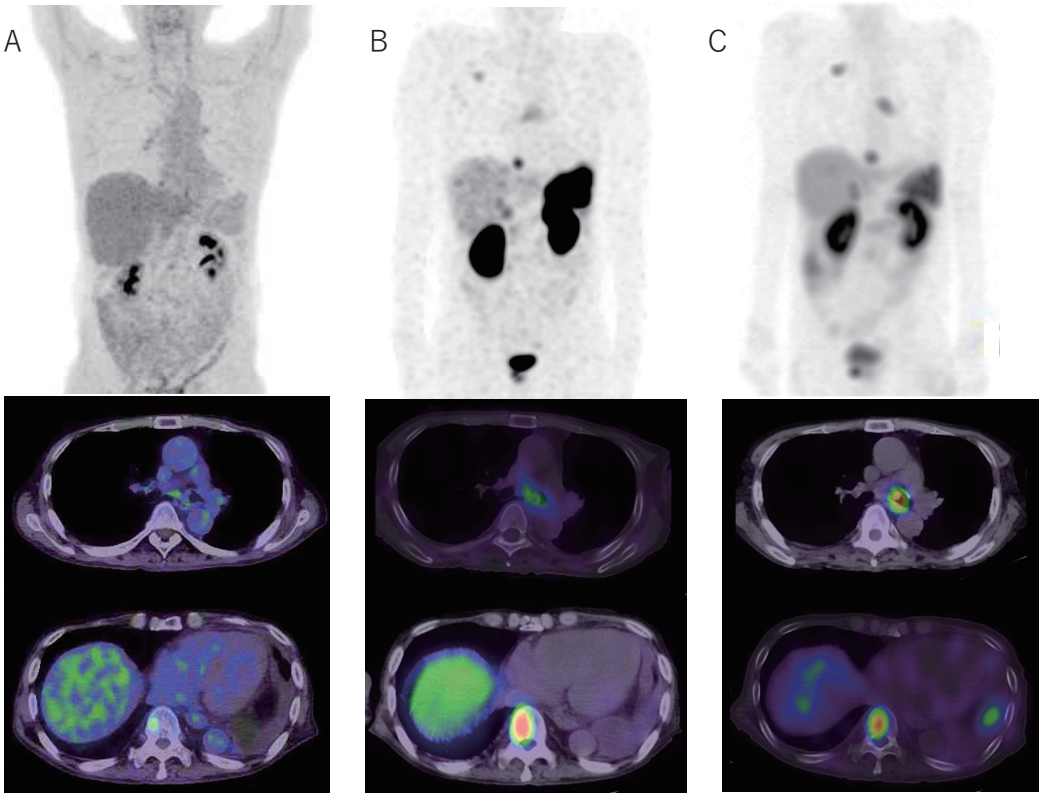

Fig. 2 ^{177}Lu-DOTATATE therapy for a patient with a recurrent bronchial carcinoma, based on the authors' own case

Imaging of the bronchial carcinoma with (A) FDG-PET/CT (upper, maximum intensity projection [MIP]; lower, fused image), (B) ^{111}In-octreotide SPECT/CT (upper, MIP; lower, fused image) and (C) ^{177}Lu-DOTATATE SPECT/CT (upper, MIP; lower, fused image). A patient with a history of bronchial carcinoma was suspected of having disease recurrence. ^{18}F-FDG PET/CT revealed slight uptake in a left bronchial mass and mild uptake in the thoracic vertebrae. ^{111}In-octreotide SPECT/CT revealed uptake in these lesions with intensity equal to or greater than that of the liver. The findings from both imaging modalities suggest recurrent lesions consistent with a low-grade NET. Subsequent ^{177}Lu-DOTATATE SPECT/CT, acquired approximately 24 h after injection, revealed intense uptake in the same regions corresponding to the ^{111}In-octreotide–avid lesions, indicating the potential for a favorable therapeutic response to ^{177}Lu-DOTATATE.

^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

SPECT/CT: single photon emission computed tomography/CT

Pheochromocytomas and paragangliomas

Pheochromocytomas and paragangliomas (PPGLs) originate from chromaffin cells in the adrenal medulla and extra-adrenal paraganglia, respectively,[64] with an estimated annual incidence of 0.8 per 100,000 individuals.[65] Common presenting symptoms include palpitations, hypertension, excessive sweating, and headaches. Surgical resection remains the mainstay and potentially curative treatment option for localized or nonmetastatic paragangliomas. However, malignant progression occurs in approximately 10% of pheochromocytomas and 15–35% of extra-adrenal paragangliomas, often resulting in recurrence or distant metastasis despite initial radical treatment.[66-68]

Radionuclide therapy with [^{131}I]-meta-iodobenzylguanidine (^{131}I-MIBG) has been used since the

1980s to treat metastatic paragangliomas. Approximately one-third of patients achieve radiographic response, and 43% experience disease stabilization,[69] with a median OS of 4.7 years.[70] A meta-analysis involving 243 patients treated with ^{131}I-MIBG showed an ORR of 30% (CR, 3%; PR, 27%) and DCR of 82% (SD, 52%).[71] However, the therapy is associated with notable adverse effects, including hypertension, hypothyroidism, and gastrointestinal and hematological toxicities, which can limit its broader use.[72] Currently, ^{123}I-MIBG is favored for diagnostic imaging due to its superior imaging quality, whereas ^{131}I-MIBG remains primarily used in therapeutic and theranostic applications.[73]

PPGLs are NETs that generally express SSTR, particularly SSTR2 and SSTR3; however, they are negative for SSTR1, SSTR4, and SSTR5. SSTR2 expression is notably associated with specific genetic alterations, such as mutations in the succinate dehydrogenase subunit B (SDHB) gene. Moreover, elevated SSTR2 expression has been correlated with metastatic disease, irrespective of the SDHB/SDHx mutation status.[74]

^{68}Ga-DOTATATE PET/CT is the preferred functional imaging modality, demonstrating superior diagnostic performance compared with ^{131}I-MIBG single photon emission computed tomography (SPECT)/CT. It is particularly effective in detecting extra-adrenal sympathetic paragangliomas and metastatic and multifocal PPGLs.[75,76]

The detection rates of ^{68}Ga-DOTA-conjugated SSTR-targeting peptide PET were consistently higher, with a pooled estimate of 93%, than other imaging modalities, and it is prominent in imaging head and neck paragangliomas.[77]

Considering SSRT as a potential target for PPGLs, several studies have reported the therapeutic efficacy of ^{177}Lu-DOTATATE in these tumors. In 201 patients with inoperable or metastatic PPGLs treated with PRRT using ^{90}Y, ^{177}Lu, or a combination of both, an overall ORR of 26% was achieved, and the DCR was 83%. ^{177}Lu-DOTATATE had an ORR of 26% and a DCR of 83%. Clinical and biochemical responses were observed in 61% and 64% of the patients, respectively. Comparable tumor response rates were reported for both ^{90}Y- and ^{177}Lu-based PRRT agents. Treatment-related adverse events were generally mild, with grade 3/4 neutropenia, thrombocytopenia, lymphopenia, and nephrotoxicity occurring in 3%, 9%, 11%, and 4% of patients, respectively.[78]

In a comparative study involving 22 patients with progressive or metastatic pheochromocytoma or paraganglioma, patients were treated with either ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, or ^{131}I-MIBG. Those who received PRRT exhibited improved PFS and treatment response compared with those treated with ^{131}I-MIBG; however, no significant difference in OS was confirmed.[79]

A separate retrospective analysis involving 22 patients (2 with localized and 20 with metastatic disease) treated with ^{177}Lu-DOTATATE PRRT demonstrated a median OS of 49.6 months and a median PFS of 21.6 months. A scintigraphic response of >50% was observed in 47% of the patients. Furthermore, 40% of the patients exhibited a biochemical response of >50% and a chromogranin Ki-67 index of <15%, which was significantly associated with longer OS and PFS.[80]

The ESMO-EURACAN guidelines for adrenocortical carcinomas and malignant phaeochromocytomas published in 2020 recommend an individualized management approach in cases of disease progression, including consideration of ^{177}Lu-DOTATATE alongside chemotherapy, local interventions, and other systemic treatments.[81] ^{177}Lu-DOTATATE may be considered when the radiotracer uptake by the target lesion is higher by SSTR imaging than by ^{123}I-MIBG. If both imaging modalities show adequate uptake, sequential treatment using the alternative radiopharmaceutical may be considered.[82] Importantly, treatment selection should not rely solely on phenotypic imaging. Patient-specific factors (eg, age, prior therapies, and bone marrow reserve) and tumor characteristics (eg, burden, anatomical location, secretory activity, and growth kinetics) are considered to determine the appropriate therapeutic strategy.[83]

Up to 50% of metastatic PPGLs homogeneously overexpress the targets of ^{177}Lu-DOTATATE and ^{131}I-MIBG therapies, whereas overexpression is heterogeneous in 25%.[84] There is a trend to administer ^{131}I-MIBG earlier and predominantly in PCCs. Prado-Wohlwend et al reported a PFS of 25.43 months for ^{131}I-MIBG and 29.55 months for ^{177}Lu-DOTATATE, with no statistically significant difference between the two approaches. However, in the regression model, ^{131}I-MIBG was associated with an approximately 10-month shorter PFS than ^{177}Lu-DOTATATE, a difference that was particularly pronounced in patients with pheochromocytomas.[85]

^{177}Lu-DOTATATE therapy (mean of four cycles, mean administered total cumulative dose: 24.42 GBq per patient) was applied for ^{131}I-MIBG-negative PGL with progressive/symptomatic locally advanced or metastatic disease. Following PRRT, symptomatic improvement was observed in 89% (CR, 4; PR, 2; SD, 2; PD, 1). The biochemical response revealed PR in 2, SD in 4, and PD in 3 of the 9 patients. The DCR based on molecular imaging was 67% (PR, 4; SD, 2; PD, 3), and that based on RECIST 1.1 was 67% (PR, 1; MR, 2; SD, 3; PD, 3). PFS was 63%, and OS was 65% at 40 months. Tolerability was favorable with grade I side effects.[86] Table 4 presents the key studies.

Table 4 Key clinical reports on PRRT for pheochromocytomas and paragangliomas

Study	Subjects number	Treatment	Cumulative activity	Response	PFS (months)	OS (months)	Toxicity/notes
Satapathy et al,[78] 2019 (Meta-analysis)	201	^{90}Y/^{177}Lu-DOTATATE	–	ORR, 25%; DCR, 84%	–	–	Grade 3/4, neutropenia 3%; thrombocytopenia 9%; lymphopenia 11%; nephrotoxicity 4%
Vyakaranam et al,[80] 2019 (Retrospective analysis)	22 (2 localized; 20 metastatic)	^{177}Lu-DOTATATE	29.6 GBq (range, 22.2–81.4)	Scintigraphic response >50%, 47%; Biochemical >50%, 40%	21.6	49.6	Grade 1–2 hematologic toxicities and no kidney toxicity
Prado-Wohlwendl et al,[85] 2022 (Meta-analysis)	608 (264 pheochromocytomas; 316 paragangliomas; 28 not specified)	^{177}Lu-DOTATATE, ^{131}I-MIBG	^{177}Lu-DOTATATE, 22–29.6 GBq ^{131}I-MIBG, 7.4–39.4 GBq	–	29.55 (^{177}Lu-DOTATATE) 25.43 (^{131}I-MIBG)	–	–
Parghane et al,[86] 2021	9 (^{131}I-MIBG-negative cohort)	^{177}Lu-DOTATATE	24.42 GBq	Symptomatic CR, 4; PR, 2; DCR (imaging), 67%	63% at 40 months	65% at 40 months	Grade I

PRRT: peptide receptor radionuclide therapy
PFS: progression free survival
OS: overall survival
DCR: disease control rate
ORR: objective response rate
PR: partial response
CR: complete response
^{131}I-MIBG: [^{131}I]-meta-iodobenzylguanidine

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Children

On April 23, 2024, the US Food and Drug Administration approved ^{177}Lu-DOTATATE for the treatment of pediatric patients (aged ≥12 years) with SSTR-positive GEP-NETs, including foregut, midgut, and hindgut tumors. This decision was supported by pharmacokinetic, dosimetry, and safety data from the NETTER-P study—an international, multicenter, open-label, single-arm trial. Efficacy was extrapolated from the NETTER-1 trial, a randomized, multicenter, open-label, active-controlled study that involved 229 adult patients with locally advanced, inoperable, or metastatic SSTR-positive midgut carcinoid tumors. In the NETTER-P study, safety was assessed in nine pediatric patients, including four with GEP-NETs.[87] Investigators reported that the safety profile in children was consistent with that observed in adults in the NETTER-1 trial. Furthermore, dosimetry analyses indicated that the radiation AD in pediatric patients remained within the established organ dose thresholds for external beam radiation therapy and was comparable to that observed in adults receiving the approved ^{177}Lu-DOTATATE regimen. The recommended pediatric dose of ^{177}Lu-DOTATATE is 7.4 GBq administered every 8 weeks for four doses. Premedication and concomitant administration with 2.5% lysine–arginine amino acid solution are recommended according to established protocols.[88]

A study evaluated the safety and efficacy of ^{177}Lu-DOTATATE combined with low-dose oral capecitabine as a radiosensitizer in pediatric and young adult patients with metastatic or inoperable NETs.[89] Capecitabine is an oral fluoropyrimidine prodrug that is preferentially activated to 5-fluorouracil in tumor cells due to higher levels of thymidine phosphorylase (TP), which reduces systemic toxicity while enhancing tumor-specific cytotoxicity. Radiation therapy can further upregulate TP expression, leading to a synergistic antitumor effect when combined with capecitabine.[90,91] Nineteen patients (14 with GEP-NETs and 5 with other NET subtypes) received 65 treatment cycles, ranging from 1 to 6 cycles per patient, with a median cumulative activity of 600 mCi (range, 100–1000 mCi). The ORR was 41%, and the DCR was 94%. Grade 1 and 2 adverse events were observed in 74% and 26% of the patients, respectively. During a median follow-up of 80.1 months, 21% of the patients experienced disease progression, and 21% died. The estimated 5-year PFS and OS rates were 54% and 63%, respectively.[89]

Neuroblastoma

Neuroblastoma is the most common extracranial solid malignancy in early childhood, typically diagnosed at a median age of 17–18 months. Its incidence peaks within the first year of life and decreases with age. Originating from neural crest-derived tissues—most commonly the adrenal glands or along the sympathetic nervous chain—neuroblastoma accounts for approximately 8%–10% of all pediatric cancers.[92-94] Prognosis varies widely according to the age at diagnosis, extent of disease, and tumor biology.[95] At least half of patients with neuroblastoma are at high risk. Although effective salvage therapies are available for low- to intermediate-risk disease, including localized relapse, no standard salvage regimen has been established for recurrent or refractory multifocal disease in high-risk patients, where survival remains approximately 50% despite intensive multimodal treatment, such as surgery, chemotherapy, radiotherapy, or autologous stem cell reinfusion.[96,97]

Neuroblastoma is known to be radiosensitive, and radionuclide therapy with ^{131}I-MIBG has been used in since the mid-1980s for treating relapsed or refractory cases. ^{131}I-MIBG remains a widely used therapeutic option in this setting, with response rates ranging from 20% to 40%.[98,99] However, outcomes have varied significantly due to differences in administered radiation doses and methods of response assessment. Recently, clinical trials have begun exploring combination therapies that incorporate ^{131}I-MIBG with cytotoxic chemotherapy, anti-GD2 immunotherapy, and immune checkpoint inhibitors, such as anti-PD-1 agents.[97]

Autoradiography and immunohistochemical analyses have demonstrated SSTR expression in approximately 77%–89% of neuroblastoma cells, with SSTR2 being the most frequently expressed subtype, even in recurrent or primary refractory tumors.[100-102]

The diagnostic performance of ^{123}I-MIBG scintigraphy in neuroblastoma is well established, with a sensitivity and specificity of approximately 90%, respectively.[103,104] ^{68}Ga-DOTATATE PET/CT has emerged as a promising alternative, contributing to initial staging, recurrence detection, and therapeutic planning, and may offer superior sensitivity and specificity compared with MIBG imaging.[104-108] In patients with neuroblastoma, both ^{68}Ga-DOTATATE PET/CT and ^{131}I-MIBG SPECT/CT exhibited a sensitivity of 100% on a per-patient basis; however, ^{68}Ga-DOTATATE PET/CT detected 52 lesions, compared with 30 lesions identified by ^{131}I-MIBG SPECT/CT in a per-lesion analysis.[109]

In terms of radiation exposure, the effective dose of ^{123}I-MIBG is approximately 0.013 mSv/MBq, which is lower than that of ^{68}Ga-DOTATATE (0.021 mSv/MBq). However, the radiation dose of ^{68}Ga-DOTATATE can be further minimized using the standardized European Association of Nuclear Medicine weight-based activity calculator.[110,111] Moreover, this effective dose remains significantly lower than that of ^{111}In-pentetreotide, which is approximately 0.073 mSv/MBq.[112]

^{177}Lu-DOTATATE therapy is conceptually analogous to the well-established ^{131}I-MIBG therapy because both therapies deliver targeted β-emitting radionuclides to neuroblastoma lesions. However, they differ in both the targeting molecule and the radioisotope used for delivering radiation to the tumor cells.

In a pilot study that included six pediatric patients (aged 2–14 years) with relapsed or primary refractory neuroblastoma, Gains et al reported that all patients demonstrated ^{68}Ga-DOTATATE-avid lesions (with uptake greater than that of the liver). Each patient received 2–3 cycles of ^{177}Lu-DOTATATE, with treatment intervals ranging from 9 to 14 weeks (median, 9 weeks) and a median administered activity of 7.3 GBq per cycle.

According to the RECIST criteria, five patients achieved SD, and one had PD. Two of the five SD cases exhibited metabolic responses and tumor shrinkage, with one patient exhibiting a persistent partial metabolic response and sustained lesion size reduction.

In terms of toxicity, three patients experienced grade 3 thrombocytopenia following two cycles, and one patient developed grade 4 thrombocytopenia after the second cycle. Importantly, no significant renal toxicity was observed in any patient.[113]

Kong et al investigated the use of ^{68}Ga-DOTA-octreotate PET/CT and PRRT in pediatric patients with refractory metastatic neuroblastoma. In a cohort of eight children (aged 2–9 years), ^{68}Ga-DOTA-octreotate PET/CT identified additional lesions in 38% of the cases compared with either diagnostic ^{123}I-MIBG scans (n = 5) or posttreatment ^{131}I-MIBG scans (n = 3), both conducted with SPECT or SPECT/CT. Of these patients, four (aged 3–9 years) received PRRT, using various radiopharmaceuticals: ^{111}In-DOTATATE in 10 treatments, ^{177}Lu-DOTATATE in 5, one patient received a combination of ^{111}In and ^{177}Lu-DOTATATE, and another received combined ^{177}Lu and ^{90}Y-DOTATATE. No significant acute toxicities were observed during or shortly after administration. Delayed adverse effects were mainly hematological and were manageable with supportive care with no long-term clinical complications. All patients exhibited objective clinical responses.

Two patients remained alive at 40 and 56 months after PRRT initiation. Two others succumbed to disease progression: one approximately 2 months after therapy despite early symptomatic and partial imaging response and the other after 19 months, following a sustained symptomatic improvement for over a year.

Although the sample size was limited, the median best PFS following PRRT was estimated

to be 10.5 months (range, 2–20 months).[105] In a separate study, Fathpour et al assessed the therapeutic impact of ^{177}Lu-DOTATATE combined with chemotherapy in pediatric patients with refractory neuroblastoma. Among 14 patients (aged 4–9 years), ^{68}Ga-DOTATATE PET/CT was positive in 71.4%, with a median of two lesions detected. Five patients who were refractory or relapsed after ^{131}I-MIBG therapy and exhibited intense uptake on ^{68}Ga-DOTATATE PET/CT received ^{177}Lu-DOTATATE in combination with chemotherapeutic agents, with a median administered activity of 13.69 GBq (range, 3.7–24.8 GBq). Of these, two achieved CR but relapsed within 6 months, one achieved PR, and two had PD. The estimated OS, based on Kaplan–Meier analysis, was 14.5 months. The reported treatment-related toxicities were mild, consisting of grade 1–2 leukopenia, anemia, and thrombocytopenia and grade 1 elevations in serum creatinine.[114]

The Phase IIa LuDO trial evaluated ^{177}Lu-DOTATATE therapy in children with refractory metastatic high-risk neuroblastoma, using an activity of 75–100 MBq/kg per course, administered at 8–12-week intervals. Among the 14 evaluable patients, no objective responses were observed 1 month after treatment, with a median PFS of 2.96 months and a median OS of 13.0 months.[115] Therefore, the trial did not proceed to the second stage. The measured renal radiation dose was below the target in all cases, with a median value of approximately 70% of the 23-Gy objective, primarily due to rapid disease progression in many patients. This suggests that a more intensified dosing schedule could have allowed for higher administered activity in most participants.[97]

Building on these findings, the trial was followed by the LuDO-N trial, a multicenter phase II clinical study investigating ^{177}Lu-DOTATATE for treating recurrent or relapsed high-risk neuroblastoma in children. The LuDO-N trial adopted an intensified dosing regimen, delivering two doses over 2 weeks to better address the typically aggressive nature of the disease. The primary objective was to evaluate tumor response at 1 and 4 months after treatment, and the secondary endpoints included assessments of OS and treatment-related toxicity.[97]

The role of patient-specific dosimetry in guiding the number of treatment cycles or administered activity per cycle in radionuclide therapy remains an area of active debate. Although fixed-activity protocols remain commonly employed, initial dosing is often adjusted based on tumor burden, renal function, body weight, or other clinical parameters. Recent findings regarding the "tumor sink effect" (an inverse relationship between renal and tumor uptake of ^{68}Ga-DOTATATE in patients with SSTR2-positive NETs) further support the need for individualized treatment planning.[116]

Malcolm et al reported that during multicycle ^{177}Lu-DOTATATE therapy, the tumor's contribution to the AD tended to decrease with each successive cycle, whereas the renal effective half-life remained relatively constant. Their patient-specific dosimetry simulations from a clinical trial emphasize the importance of accounting for inter-cycle changes in the tumor AD and biokinetics, particularly when personalizing administered activity in pediatric patients. This approach may be particularly relevant in the context of PRRT for radiation-sensitive tumors, such as neuroblastoma.[117]

Table 5 presents the type of study associated with ^{177}Lu-DOTATATE for each article cited in this review.

Table 5 The type of study related to ^{177}Lu-DOTATATE for each article cited in this review

Type of study	Type of disease				
	Thyroid cancer	Meningioma	Bronchial carcinoma	Pheochromocytomas and paragangliomas	Children and neuroblastoma
Prospective study		Kurz et al,[39] 2024 (clinical trial)	Ianniello et al,[48] 2016 (clinical trial) Kim et al,[60] 2020 (clinical trial) Hallqvist et al,[61] 2025 (clinical trial)		NETTER-P,[88] 2021 (clinical trial), Sundquist et al,[97] 2022 (clinical trial), Gains et al,[113], 2011 Fathpour et al,[114] 2021, Gains et al,[115] 2020 (clinical trial)
Retrospective study	Basu et al,[26] 2020	Severi et al,[40] 2024 Amerein et al,[41] 2024	Brabander et al,[49] 2017, Mariniello et al,[51] 2016, Mirvis et al,[52] 2020, Zandee et al,[53] 2021, Parghane et al,[54] 2017, Zidan et al,[56] 2022	Vyakaranam et al,[80] 2019, Prado-Wohlwend et al,[84] 2022, Parghane et al,[86] 2021	Aggarwal et al,[89] 2024, Kong et al,[105] 2016, Malcolm et al,[117] 2022
Review	Maghsoomi et al,[24] 2021 Grossrubatscher et al,[25] 2020	Boursier et al,[42] 2024	Ma et al,[50] 2022	Satapathy et al,[78] 2019, Crona et al,[82] 2017, Jha et al,[83] 2021, Prado-Wohlwend et al,[85] 2022	
Meta-analysis		Mirian et al,[38] 2021		Satapathy et al,[78] 2019	
Case report			Escala Cornejo et al,[63] 2018		

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CONCLUSION

^{177}Lu-DOTATATE has exhibited significant clinical efficacy in the treatment of advanced GEP-NETs. Considering the widespread expression of SSTRs in various neuroendocrine and neuroendocrine-like tumors—including pheochromocytomas, paragangliomas, meningiomas, medullary thyroid carcinomas, neuroblastomas, and bronchial NETs—the therapeutic potential of ^{177}Lu-DOTATATE extends beyond the GEP-NET setting. To clarify the potential of ^{177}Lu-DOTATATE across SSTR-expressing malignancies, further prospective studies with larger patient populations, standardized protocols, and long-term follow-up are warranted. Furthermore, future studies must prioritize the development of pediatric-specific endpoints and the identification of predictive biomarkers, such as molecular profiles and functional imaging markers, to enable more personalized treatment strategies. Ongoing early-phase trials are anticipated to lay the groundwork for these future advancements.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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