



Efficacy and safety of ^{225}Ac -DOTATATE targeted alpha therapy in metastatic paragangliomas: a pilot study

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Abstract

Purpose In this study, we aim to evaluate the efficacy and safety of ^{225}Ac -DOTATATE targeted alpha therapy in advanced-stage paragangliomas (PGLs).

Methods Nine (6 males and 3 females) consecutive patients with histologically proven PGLs were treated with ^{225}Ac -DOTATATE targeted alpha therapy (TAT) and concomitant radiosensitizer, capecitabine, at 8-weekly intervals up to a cumulative activity of ~74 MBq. The primary endpoint included evaluating therapy response and disease control rate (DCR) using the RECIST 1.1 criteria. Additional secondary endpoints comprised clinical response assessment using EORTC QLQ-H&N35 questionnaire, Karnofsky Performance Scale (KPS), Eastern Cooperative Oncology Group performance status (ECOG), analgesic score (AS), dose alterations of anti-hypertensive drugs (anti-HTN), and the safety and side-effect profile evaluation as per CTCAE criteria version 5.0.

Results Following ^{225}Ac -DOTATATE treatment, morphological response revealed partial response in 50%, stable disease in 37.5%, and disease progression in 12.5%, with a DCR of 87.5%. Similarly, the symptomatic response was remarkable, and anti-HTN drugs were stopped in 25% and reduced in 37.5%. Another significant finding in our study revealed a morphologic DCR of 66.6% (2/3) in patients who failed previous lutetium-177 peptide receptor radionuclide therapy (^{177}Lu -PRRT). Regarding the KPS, ECOG, and AS performance scores, a notable improvement was observed post- ^{225}Ac -DOTATATE treatment. The QLQ-H&N35 symptom scores evaluated in seven H&N PGL patients showed significant improvement in all aspects. No improvement in sexual function was noted ($P=0.3559$). Despite the significant reduction in the analgesic score post-treatment ($P=0.0031$), the QLQ-H&N35 revealed only marginal significance concerning the intake of pain killers ($P=0.1723$). No grade III/IV hematological, renal, and hepatological toxicities were noted.

Conclusion The evidence from this study suggests ^{225}Ac -DOTATATE therapy is effective and safe in the treatment of advanced-stage PGLs and also reports a clear benefit even in patient's refractory to the previous ^{177}Lu -PRRT.

Keywords ^{225}Ac -DOTATATE therapy · Targeted alpha therapy · Paraganglioma

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Introduction

Paragangliomas (PGLs) are catecholamine secreting neuroendocrine tumors that originate from the chromaffin cells of the neural crest-derived sympathetic and parasympathetic paraganglia. While sympathetic paragangliomas are located from the superior cervical ganglion up to the pelvic region, the parasympathetic PGLs originate from the carotid bodies, jugulotympanic, and vagal paraganglia and are found in the head and neck (H&N) region [1]. Management of paragangliomas involves an individualistic patient-based approach with only close surveillance in asymptomatic patients. For amenable, localized, and recurrent tumors, the local tumor

management by surgery is the best curative and cytoreductive approach [2].

Another option for inoperable localized tumors is external beam radiotherapy (EBRT). A study summarizing 34 published series on head and neck paragangliomas (H&NPGLs) observed a local symptomatic tumor control with EBRT in more than 70%, with partial/complete resolution in approximately 60% of the cases [3–6]. However, as 25% of the PGLs are malignant [7] and the estimated 1-year progression-free survival of treatment-naïve malignant PGLs was 46% [8], systemic treatment approaches for the treatment of metastatic disease have been considered depending on the clinical situation [8].

At present, there is no definitive treatment regimen for the type of chemotherapy to be executed in metastatic PGL patients. However, cyclophosphamide, vincristine, and dacarbazine (CVD) are the most common and effective regimens used in rapidly progressing PGLs. In this context, a long-term 22-year follow-up study after CVD treatment has shown a response rate in 55% of the patients but did not differ in the overall survival (OS) between patients who responded to CVD and those who did not. Hence, chemotherapy favors only symptomatic response and does not have an impact on survival [9]. The role of tyrosine kinase inhibitors such as sunitinib is preliminary and not yet established, with only a few case reports demonstrating symptomatic response [10].

It has been more than two decades now since ^{131}I MIBG therapy has been adopted for the management of patients with metastatic PGLs. In clinical practice, ^{131}I -MIBG is predominantly the treatment of choice in slow-growing sympathetic PGLs and pheochromocytomas (PCCs) [11–13]. A phase II trial by Gonas et al. [14] included a modest number of 34 PGL patients who were treated with high-dose ^{131}I -MIBG (mean cumulative activity: 388 mCi). Although their results favor the treatment of ^{131}I -MIBG for PCC and PGL, they observed that only 20.6% (7/34) patients showed complete or partial response (CR/PR), and the remaining majority of 79.4% experienced either stable or progressive disease (SD/PD).

A recent multicentric phase II study led to the FDA approval of HSA ^{131}I -MIBG (Ultratrace, *Azedra*) in the USA [15]: 68 patients received at least one and 50/68 patients received two doses of HSA [^{131}I]MIBG. Of the 68 patients who received at least one therapeutic dose of HSA ^{131}I -MIBG, 17 (25%) had a durable reduction in baseline anti-hypertensive medication use. Of the 64 patients with the evaluable disease, most patients showed partial responses (23%, 15/64) or stable disease (44/64, 69%). The median OS was 36.7 months (95% confidence interval, 29.9–49.1 months) with 18 months for patients who received one therapeutic dose and 44 months for those who received two therapeutic doses [15].

As most of the PGLs express somatostatin receptor subtype 2 (SSTR2), the results of ^{177}Lu -DOTATATE therapy have been encouraging and have been extensively implemented into the therapeutic regimen for H&NPGLs [16–18]. Nastos et al. [18] treated PCC/PGL patients with either ^{131}I -MIBG, ^{90}Y -DOTATATE, or ^{177}Lu -DOTATATE, and survival results revealed that PRRT treatment offers increased OS, progression-free survival (PFS), event-free survival (EFS), and response to treatment compared to ^{131}I -MIBG therapy in patients with progressive/malignant PGLs.

^{177}Lu -DOTATATE has been approved by the Food and Drug Administration (FDA) in the USA and European Medical Agency (EMA) for midgut Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs). The role of peptide receptor radionuclide therapy (PRRT) was specifically demonstrated in the NETTER I phase III randomized control trial, where ^{177}Lu -PRRT resulted in a significantly longer PFS and overall survival (OS) in midgut GEP-NET patients [16]. The same is advocated for PGLs who do not show reasonably good uptake in diagnostic $^{131/123}\text{I}$ -MIBG whole-body scans.

More recently, Yadav et al. [17] focused on the survival benefits of 25 PGL patients treated with ^{177}Lu -PRRT + radiosensitizing oral chemotherapy with capecitabine and showed that 28% of patients achieved radiological response and 43% had a symptomatic response as well. Another retrospective study by Kong et al. [19] in 20 pheochromocytoma/paraganglioma (PPGL) patients demonstrated a prolonged PFS of 34 months, while the median OS was not attained. The first prospective phase II trial was conducted to examine the safety and efficacy of ^{90}Y -DOTATOC in 11 PCCs and 28 PGLs. Radiologic, biochemical, and clinical responses were observed in 36.5%, 18.2%, 45.5%, and 10.7%, 14%, and 21.4%, respectively, among the PCC and PGL patients. Authors reported a median OS of 32 and 82 months in PCC and PGL, respectively [20]. Severi et al. [21] analyzed 46 consecutive PPGL patients treated with ^{90}Y -DOTATOC or ^{177}Lu -DOTATATE PRRT and obtained a disease control rate of 80% in a median follow-up duration of 73 months.

^{177}Lu -DOTATATE demonstrated a promising life-extending option, albeit the heterogeneous patient population recruited by various investigators. However, approximately 14 to 19.5% are expected to develop resistance to beta-particle-based PRRT and experience disease progression [17, 19, 21].

Recently, further advances in PRRT have included the use of SSTR antagonist [22] and the application of high linear-energy transfer alpha-particle emitters that have expanded the therapeutic landscape of PRRT [23–25]. To date, the use of alpha-particle-based therapies is limited to only two reports that have used Bismuth-213, Actinium-225, and Lead-212 to treat GEP-NETs and prostate cancers [23–26].

In a recent pilot prospective study conducted at our center, ^{225}Ac -DOTATATE in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) illustrated treatment response and greater survival benefit even in patients refractory to the previous ^{177}Lu -PRRT. Among the 32 GEP-NET patients, we observed morphological response in 15/24 patients, and the remaining patients experienced disease stabilization [24]. We further studied the long-term outcome results in an extended cohort of 82 patients, and the findings are in accordance with the short-term results and remarkable in terms of achieving ORR and extending the survival of the patients [27].

The increasing evidence and encouraging preliminary results of alpha-particle therapy in GEP-NETs encouraged us to adopt the same treatment in malignant PGLs who have failed standard of care treatment options. Hence, this pilot study seeks to report the efficacy and safety results of ^{225}Ac -DOTATATE therapy in advanced-stage PGLs.

Materials and methods

Patients

We treated nine consecutive advanced-stage PGL patients with ^{225}Ac -DOTATATE TAT between July 2018 and July 2021 at the Department of Nuclear Medicine, AIIMS, New Delhi, India. The last date of follow-up analysis was August 15, 2021.

Patient inclusion and exclusion criteria

Eligibility for the ^{225}Ac -DOTATATE treatment included patients with incomplete or unresectable tumors, distant metastases, patients either treatment naïve or resistant to conventional therapies such as ^{131}I -MIBG, stable disease, or refractory disease on ^{177}Lu -PRRT, high SSTR expression on ^{68}Ga -DOTANOC PET/CT scan with a Krenning score > 3 (uptake greater than liver). Patients were excluded if baseline hemoglobin was less than 9.5 g/dL, thrombocytopenia (platelet count $< 60,000/\mu\text{L}$), leukopenia (TLC $< 3000/\mu\text{L}$), inadequate kidney (serum creatinine of greater than 1.4 mg/dL), and liver function (serum bilirubin greater than 1.2 mg/dL), life expectancy less than 6 months, Karnofsky Performance Status < 40 (KPS), Eastern Cooperative Oncology Group (ECOG) status > 3 were excluded from the study. The study was approved by the institutional ethics committee for the use of ^{225}Ac -DOTATATE in PGL patients on compassionate grounds. All patients gave written informed consent before the therapy.

The radiolabelling and ^{225}Ac -DOTATATE treatment protocol were performed according to our clinic protocol as mentioned in our previous publication [24]. In brief,

$^{225}\text{AcCl}_3$ (300 μCi) was added to DOTATATE (160 μg), sodium ascorbate buffer (pH 4) in a final volume of 1.2 mL. The reaction mixture was incubated for 20 min at 95°C and purified through a C-18 cartridge. As previously described, ^{225}Ac -DOTATATE (100 kBq/kg) body weight per cycle [3 μCi] diluted in 50 mL of saline was administered over 30 min (flow rate 1.6 mL/min). Each cycle of ^{225}Ac -DOTATATE was administered with amino acids support for kidney protection. For kidney protection, a single-day kidney protection protocol was followed, which consisted of lysine (23.3 g) and arginine (8 g) in 1 L of the amino acid mixture in water for injection solution. This cocktail was infused over 4 h, starting 30 min before the ^{225}Ac -DOTATATE infusion. Radio-sensitizing chemotherapy, oral capecitabine (1250 mg/m²) was given orally twice daily from day 0 to 14 at each cycle of ^{225}Ac -DOTATATE therapy. Before initiating amino acid infusion, pre-medications, including an antiemetic (ondansetron) and/or corticosteroid (dexamethasone), were administered and repeated if necessary. Three patients with sympathetic PGLs, patient numbers 2, 4, and 9, were not administered corticosteroids to avoid any adverse events.

Outcome endpoints

The primary endpoint of the present study was the assessment of objective response rate (ORR) and disease control rate (DCR) according to the RECIST 1.1 criteria [28].

Key secondary endpoints included clinical response assessment of the quality of life (QoL) in H&N PGLs using EORTC QLQ-H&N35 questionnaire, Karnofsky Performance Scale (KPS), Eastern Cooperative Oncology Group performance status (ECOG), and analgesic score (AS). Assessment of dose alterations of anti-hypertensive drugs was evaluated in patients with secondary hypertension. The safety and side-effect profile was assessed as per CTCAE criteria version 5.0 [29]. The QLQ-H&N35 is composed of 35 questions which are broadly categorized into seven multi-item scales comprising of 24 questions and 11 single-item scales. The answers were converted to a linear scale ranging from 0 to 100 as recommended by Fayers et al. [30], King MT [31], and Bjordal et al. [32]. A higher score indicated the presence of intense symptoms and a poor quality of life.

Follow-up

Before and at 2, 4, and 8 weeks after every cycle of ^{225}Ac -DOTATATE therapy, complete blood counts (CBC), kidney function tests (KFT), and liver function tests (LFT) were documented in all patients to assess the toxicity. Clinical parameters including blood pressure, clinical symptoms, quality of life, doses of analgesics, and anti-hypertensives were recorded at 4-weekly intervals. Patients maintained a

subject dairy and noted their symptoms which was assessed at monthly intervals.

Objective response was evaluated with diagnostic quality CT, without contrast, and performed in conjunction with ^{68}Ga -DOTANOC PET that was repeated between the 6th and 8th week after every two to three cycles of ^{225}Ac -DOTATATE treatment and at three-monthly intervals, after completion of the ^{225}Ac -DOTATATE treatment regimen.

Therapy was repeated at 8-week intervals in all patients. Treatment was stopped in patients if they demonstrated disease progression (morphological or clinical or symptomatic) during the treatment regimen or attained the maximum administered cumulative activity of 86.6 MBq (2.34 mCi) ^{225}Ac -DOTATATE therapy.

Genetic testing

Genomic DNA from peripheral blood leukocytes was extracted, and the coding exons of genes SDHB, SDHD, and SDHC were PCR-amplified and screened by sanger sequencing.

Statistical analysis

D'Agostino-Pearson Test was performed to check for normality of distribution. Continuous variables were calculated as mean, median, standard deviation (SD), standard error of the mean (SEM), range, and interquartile range. Based on the data distribution, the baseline and post-treatment parameters were compared with either paired samples *T*-test or Wilcoxon rank-sum test. $P < 0.05$ was considered as significant. MedCalc software version 20.01 was used for the statistical analysis.

Results

Patient characteristics

In this pilot study, we recruited nine PGL patients for ^{225}Ac -DOTATATE therapy. A summary of the demographic characteristics of the patients is provided in Tables 1 and 2. Six patients presented with parasympathetic, and three had sympathetic PGL with a mean age of 41 ± 10.5 years (23–65 years). The median follow-up duration was 22.5 months (IQR: 18–28 months) from the start of ^{225}Ac -DOTATATE targeted alpha therapy (TAT).

The most common sites of metastases included eight patients with lymph node metastases, followed by skeletal and lung metastases in 6 and 3 patients, respectively. Other sites of metastases included the liver, brain, and duodenum, as depicted in Table 2. Tumor involvement was confined to

Table 1 Demographic characteristics of patients

Characteristics	Value ($N=9$)
Age (years) (mean \pm SD; range)	41 ± 10.5 (23–65)
Gender	
Male	6
Female	3
Type of paragangliomas	
Sympathetic	3
Parasympathetic	6
Type of prior therapies	
Surgery	6
Chemotherapy	1
Radiotherapy	5
^{131}I -MIBG therapy	2
^{177}Lu -PRRT	7 (PD=4 and SD=3)
Baseline blood pressure (mmHg)	138 (98–210)/83 (60–115)
Anti-hypertensive drugs	8
Pulse rate (median, range)	83 (69–140)
Prior ^{131}I-MIBG therapy	
Number of therapy cycles (median, range)	3
Cumulative activity (median, IQR)	16.6 GBq (6.6 GBq/cycle)
Prior ^{177}Lu-DOTATATE therapy	
Number of therapy cycles (median, range)	6 (3–10)
Cumulative activity (median, IQR)	34.5 ± 3.9 (27.7–38.85) GBq
^{225}Ac-DOTATATE therapy	
Cumulative activity (mean \pm SD; range)	42.4 ± 27 (15.54–86.6) MBq
	[1146 \pm 728 (420–2341) μCi]
Number of therapy cycles (median, range)	3 (2–9)

the primary site in only one patient with parasympathetic PGL.

Eight patients underwent prior lines of treatments; among whom, five underwent two lines, and three underwent > 2 lines of treatment. The primary tumor was unresectable in three patients due to major arterial encasement. Seven patients received the previous ^{177}Lu -PRRT which was discontinued in four patients due to disease progression and stopped in the remaining three patients after the administration of a maximum tolerable dose of 44.4 GBq ^{177}Lu -PRRT.

Genetic mutation testing was performed in 6 patients; two had SDHD mutation, one had SDHB mutation, three were negative for the mutation, and in the remaining three patients, mutation status was unknown. Except for one, all patients were on anti-hypertensive treatment. Among the seven patients who received prior ^{177}Lu -PRRT, in four patients who experienced disease progression, blood pressure was not stabilized by both anti-hypertensives and ^{177}Lu -PRRT treatment in 3 patients. All patients with stable

Table 2 Details of each patient

Patient no	Age/sex	Location of primary tumor	Ki-67 index	Mutation status	Site of metastases	Previous treatment			Disease status on ¹⁷⁷ Lu-PRRT	Hypertension	
						Sx	RT	¹³¹ I-MIBG			
1	41/M	Lt CBT	>20	No mutation	LN's, lungs, bone, brain	+	+	-	+	PD*	Controlled on anti-HTN, no response on ¹⁷⁷ Lu-PRRT
2	43/M	Right mediasastinum	<1	SDHB-p.S163P	LN's, lungs, bone	-	-	+	+	PD*	Not controlled despite anti-HTN or ¹⁷⁷ Lu-PRRT
3	45/M	Lt jugular foramen CBT	8–10%	NA	LN's, lungs, bone	+	+	-	+	SD	Controlled on anti-HTN and, with ¹⁷⁷ Lu-PRRT
4	42/M	Lt retroperitoneal mass	NA	No mutation	LN's, liver, bone, duodenum	+	-	+	-	-	Controlled on anti-HTN
5	36/F	Rt CBT	<2%	SDHD_H50R (E2)	LN's, liver, bone	-	-	-	-	-	Controlled on anti-HTN
6	43/F	B/L CBT	1–2%	No mutation	LN's	+	-	-	+	SD	No
7	65/F	Lt CBT	3%	NA	-	-	+	-	+	SD	Controlled on anti-HTN and ¹⁷⁷ Lu-PRRT
8	23/M	Rt CBT	8–10%	SDHD_H50R (E2)	LN's, lung, bone	+	+	-	+	PD*	Not controlled despite anti-HTN or ¹⁷⁷ Lu-PRRT
9	36/M	RT hepatorenal mass encasing IVC	NA	NA	LN's	+	+	-	+	PD*	Not controlled with anti-HTN or ¹⁷⁷ Lu-PRRT

*Patients demonstrated both radiological and clinical disease progression on ¹⁷⁷Lu-PRRT

Lt, left; Rt, right; CBT, carotid body tumor; NA, not assessed; Sx, surgery; RT, radiotherapy; PRRT, peptide receptor radionuclide therapy; SD, stable disease; PD, progressive disease; anti-HTN, anti-hypertensives

disease on ^{177}Lu -PRRT had controlled hypertension and were maintained on anti-hypertensives.

Treatment and dosage

All patients received at least two cycles of ^{225}Ac -DOTATATE TAT, and 7 patients underwent ≥ 3 cycles. The mean cumulative activity injected was 42.4 ± 27 (15.54–86.6) MBq, and the median number of cycles administered was 3 (range: 2–9). The therapy cycles were discontinued in 2 patients due to progressive disease (PD) in one patient with right mediastinal mass, and the second patient refused to undergo further treatment cycles due to depression but is stable and alive at the last date of follow-up. The patient who experienced PD eventually died due to cardiac arrest, probably due to a malignant catecholamine surge.

Treatment outcome

Among the eight patients assessed, the measurement of the target lesions of each patient and the percentage change in the lesion size is enumerated as per RECIST 1.1 criteria in Table 3. No patient achieved a complete response. The best response was partial response in 4 (50%) (Fig. 1) and stable disease in 3 (37.5%) patients. One patient with sympathetic PGL experienced morphological disease progression and was also refractory to the previous ^{177}Lu -PPRT (Tables 2 and 3). The disease control rate as per RECIST 1.1 criteria was 87.5% (7/8).

On detailed analysis, among the four patients who were refractory to prior ^{177}Lu -PPRT therapy, one completed the ^{225}Ac -DOTATATE treatment regimen and experienced a partial response; two had stable disease, and one experienced disease progression, followed by death with a DCR of

Table 3 Objective response assessment in patients

Patient S.No	Target lesion	Target lesion size Baseline ^{68}Ga -DOTANOC PET/CT scan (cm)	Target lesion size Response ^{68}Ga -DOTANOC PET/CT scan (cm)	Percentage change from baseline to current measurements (%)	RECIST 1.1 response category	Remarks	
1	Lt CBT	Left upper lobe lung mass	5.2	2.8	-66.6	PR	
		Right lung mass	3.2	0			
2	Lung	Right mediastinal mass	4.7	4.9	-8.98	PD	Appearance of multiple lung nodules
		Prevascular lymph node	4.2	3.6			
3	Lt jugular foramen CBT	Lt jugular foramen CBT	4.5	4.16	-2.2%	SD	
4	Lt retroperitoneal mass	Lt retroperitoneal mass	10.9	7.2	-31	PR	
		Para-aortic LN	2.4	1.6			
5	Rt CBT	Rt CBT	3.6	1.8	-73.5	PR	Resolution of all non-target lesions
		Liver segment VIII	4	0			
		Abdominal LN	2.8	0			
6	B/L CBT	Left CBT	3.8	2.8	-30.1	PR	
		Right CBT	2.2	1.4			
7	Lt CBT	Lt CBT	3	2.7	-10	SD	
8	Rt CBT	Rt CBT	4.2	3.9	-7.14	SD	
9	Rt hepatorenal mass					NA	

Lt, left; *Rt*, right; *NA*, not assessed; *LN*, lymph node; *CBT*, carotid body tumor; *PRRT*, peptide receptor radionuclide therapy; *SD*, stable disease; *PD*, progressive disease; *anti-HTN*, anti-hypertensives

*Diagnostic quality non-contrast CT scans were performed in conjunction with ^{68}Ga -DOTANOC PET

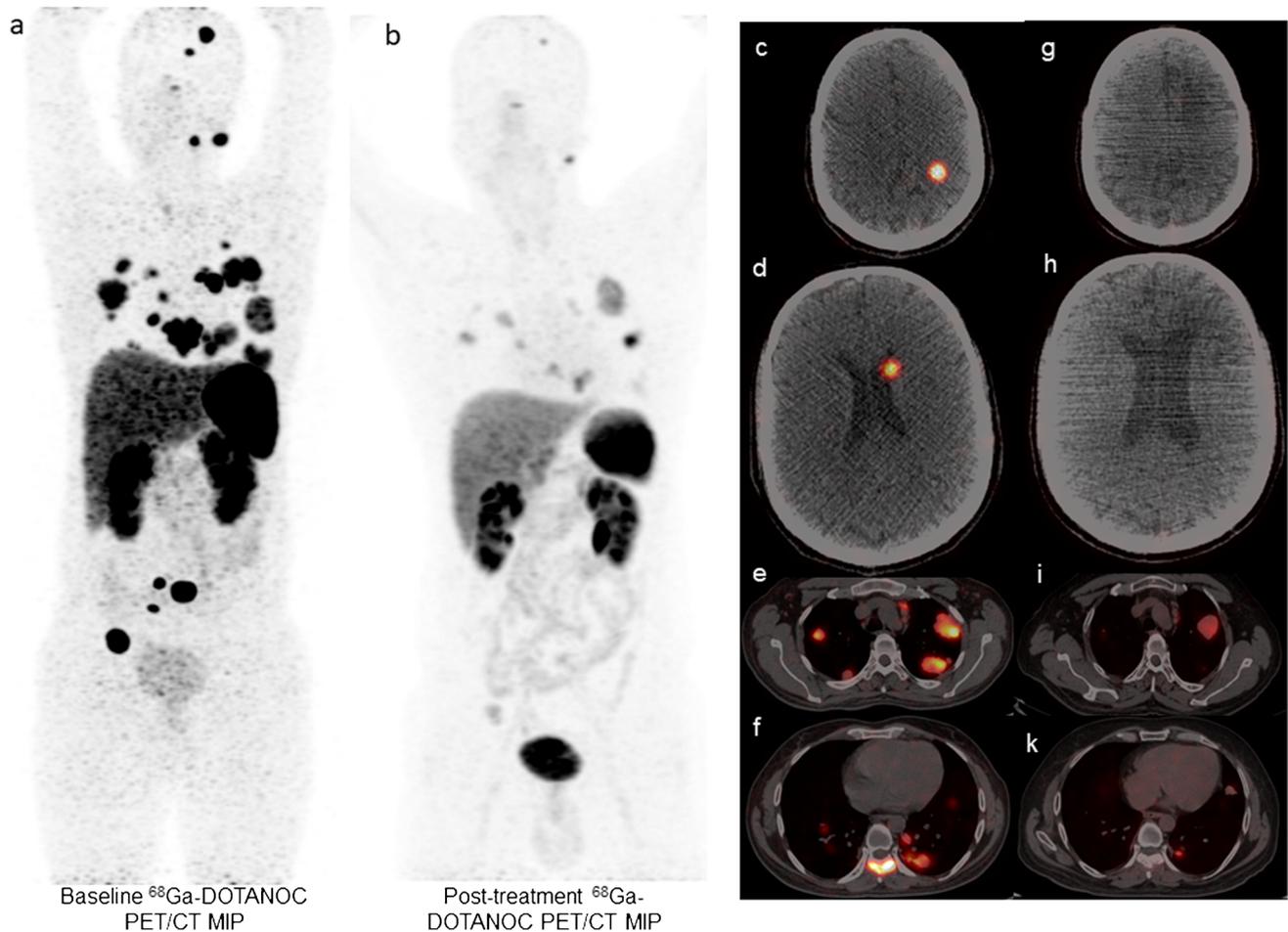


Fig. 1 A 41-year-old male patient was diagnosed with a left carotid body tumor in 2006 and underwent excision of the tumor followed by locoregional radiotherapy. The patient received multiple systemic treatments, including ^{177}Lu -PRRT and mTOR inhibitor; Everolimus, but eventually demonstrated disease progression. The baseline ^{68}Ga -DOTANOC PET/CT scan (**a**, **c–f**) demonstrates multiple lymph

nodes, bilateral lung nodules, skeletal metastases, and brain metastases involvement. Restaging PET/CT at two months after the third cycle of ^{225}Ac -DOTATATE TAT shows a remarkable reduction in all the corresponding lesions (**b**, **g–k**). (Note that the greyscale of the MIP and the PET/CT images between two scans are set at the same SUV scale, and the threshold was >2.5 .)

66.6% (Table 4). The KPS showed remarkable improvement in patients with partial tumor regression (60 ± 7 to 85 ± 5 , $P=0.0050$). A decrease in the KPS score was observed in patients who experienced PD ($P=0.1296$). The intake of analgesics significantly decreased from 12.5 ± 4.2 to 3.28 ± 5.7 ($P=0.0068$) (Table 5).

In seven patients with H&N PGL, the detailed QLQ-H&N35 scales were compared, which is enumerated in Table 6. Overall, all the symptoms remarkably decreased after ^{225}Ac -DOTATATE therapy. A marginal de-escalation of pain killers was noted ($P=0.1723$). While there was a significant positive impact of treatment on social eating, sexual function did not improve.

Anti-hypertensives were completely stopped in the two patients who also experienced partial morphological response. Medications were reduced in three; two patients maintained the same dosage as the baseline. One patient

discontinued ^{225}Ac -DOTATATE due to depression and later required anti-HTN dose escalation (Supplementary Table 1). The median time for dose reduction of anti-HTNs after the initiation of ^{225}Ac -DOTATATE TAT was 6 months (IQR: 5 to 7.2 months).

Toxicity

No side effects were observed due to concomitant Capecitabine treatment. None of the patients experienced tumor lysis syndrome or life-threatening hypertension disorders. Pre-existing grade I and II anemia was present in four and three patients, but no worsening was noted during the course of treatment. Grade I thrombocytopenia was noted in two patients at the baseline and normalized over time. No grade III/IV hematological, kidney function, and liver toxicities were manifested with no difference in the baseline and

Table 4 Details of PRRT and follow-up

Patient no	Prior ¹⁷⁷ Lu-PRRT	Disease status on prior ¹⁷⁷ Lu-PRRT	Gap between ¹⁷⁷ Lu-PRRT and ²²⁵ Ac-DOTATATE (months)	No. ²²⁵ Ac-DOTATATE cycles	Cumulative activity (MBq)	Current status on ²²⁵ Ac-DOTATATE therapy	Objective response (RECIST 1.1)	Follow-up duration (months)
1	+	PD	3	9	86.6	Completed	PR	30
2	+	PD	6	3	28.3	Discontinued	PD	19
3	+	SD	11	3	25	Ongoing treatment	SD	20
4	–	–	Not applicable	6	55.5	Ongoing treatment	PR	25
5	–	–	Not applicable	8	71	Completed	PR	24
6	+	SD	9	8	65	Ongoing treatment	PR	30
7	+	SD	12	2	15.5	Ongoing treatment	SD	12
8	+	PD	3	2	17.7	Discontinued (self)	SD	23
9	+	PD	5	2	17.7	Ongoing treatment	NA	8

PR, partial response; SD, stable disease; PD, progressive disease; anti-HTN, anti-hypertensive drugs, NA, not assessed

Table 5 Clinical response scores at baseline and post-²²⁵Ac-DOTATATE treatment

Laboratory parameters	Baseline (mean ± SD)	Post-therapy (mean ± SD)	p-value
KPS (in PR patients)	60 ± 7	85 ± 5	0.0050
KPS (in SD patients)	55 ± 7	70 ± 14	0.2048
KPS (in PD patients)	63.3 ± 5.7	30 ± 26.4	0.1296
*Analgesic score	12 (range: 4–16)	2 (0–16)	0.0031
*ECOG status	3 (range: 2–4)	1 (range: 1–2)	0.0010

KPS, Karnofsky Performance Status; ECOG, Eastern Cooperative Oncology Group performance status; PR, partial response; SD, stable disease; PD, progressive disease; anti-HTN, anti-hypertensive drugs

*Values are detailed in terms of median and range

post-treatment laboratory parameters (Table 7 and Supplementary Table 2). Among the nine patients, three patients experienced grade I/II nausea, stomach discomfort, and diarrhea during the amino acid infusion, which was reduced within 24 h of treatment. One patient experienced palpitation during the ²²⁵Ac-DOTATATE infusion but was controlled and managed with beta-blockers and an extremely slow infusion rate of ²²⁵Ac-DOTATATE.

Discussion

This study detailed the efficacy and safety results of ²²⁵Ac-DOTATATE targeted alpha therapy in metastatic PGL patients. Based on the RECIST 1.1 criteria, none of the patients had a complete response from treatment. Our study reported a notably higher ORR of 50% with ²²⁵Ac-DOTATATE TAT compared to a pooled proportion of 25% (95% CI: 19–32%) by a recent meta-analysis on ¹⁷⁷Lu-PRRT in

PPGLs [33]. On the other hand, the DCR in our study was 87.5% and was comparable to a pooled proportion of 84% (95% CI: 77–89%) with ¹⁷⁷Lu-PRRT, as reported by Sathpathy et al. [33]. Probably, the inherent slow-growth rate of PGLs may majorly contribute to the high and similar DCRs with both actinium-225 and lutetium-177 DOTATATE treatment. However, the findings should be interpreted with caution as the comparison is not ideal pertaining to heterogeneities in the type of paragangliomas, the difference in the treatment strategies, and the disease burden across the studies. The current pilot results warrant a high-level evidence head-to-head comparison randomized-controlled study between the radiotracers.

One promising finding in our study revealed that ²²⁵Ac-DOTATATE therapy induced a morphologic DCR of 66.6% even in the worst prognosis patients who were refractory to ¹⁷⁷Lu-PRRT and remarkably reduced the clinical symptoms. In addition to the encouraging radiological response, ²²⁵Ac-DOTATATE therapy induced a remarkable high

Table 6 EORTC QLQ-H&N35 scoring at baseline and end of analysis in 7 H&N PGL patients

Variables	Baseline QLQ (mean ± SD)	Post-therapy QLQ (mean ± SD)	P-value
Pain	80.9 ± 17.8	28.5 ± 23	0.0002
Swallowing	80.9 ± 17.8	1.31 ± 16.6	0.0010
Senses (taste and smell)	66.6 ± 19.2	9.52 ± 16.2	<0.0001
Speech	71.4 ± 12.5	21.8 ± 17.2	<0.0001
Social eating	80.9 ± 17.5	19.04 ± 32.5	0.0004
Social contact	100	28.5 ± 12.5	<0.0001
Sexuality	100	90.4 ± 12.5	0.3559
Teeth	52.3 ± 33.3	9.52 ± 16.2	0.0002
Opening mouth	71.4 ± 12.5	19.04 ± 17.8	0.0002
Dry mouth	66.6 ± 33.3	19.04 ± 12.5	0.0004
Sticky saliva	61.9 ± 12.5	14.2 ± 17.0	0.0004
Coughing	33.3 ± 33.3	4.76 ± 12.5	0.0453
Felt ill	7.1 ± 16.2	14.2 ± 17.8	<0.0001
Pain killer	2	1.4	0.1723
Nutritional supplement	2	1.14	0.0010

SD, standard deviation

clinical response in all patients irrespective of the progressive disease status on imaging in terms of quality of life in H&N, KPS, ECOG, and analgesic scores. The quality-of-life assessment in H&N paragangliomas indicated a significant improvement in all the scales except for sexuality observed during the ²²⁵Ac-DOTATATE therapy. Secondary HTN was effectively controlled with complete termination of anti-hypertensives in two patients (25%) and dose de-escalation in 37.5% of the patients.

Over the past few years, significant progress has been achieved in understanding PGL genetics. The SDHD

mutations are known to account for one-third of the H&NPGLs and are commonly inherited [34]. Among the four H&NPGLs patients who had genetic reports available, two patients demonstrated SDHD mutations and were sporadic. Interestingly, both patients with positive mutation status observed effective disease control in terms of clinical and radiologic assessments, including morphologic PR in one patient.

PPGLs most commonly present with hypertension, episodes of headaches in 90%, and sweating in 60–70% of the patients [7]. Among the PPGLs, unlike PCCs and sympathetic PGLs, H&NPGLs derived from the parasympathetic ganglia are often non-secretory and rarely secrete catecholamines. In the literature, only 2–3% of H&NPGL are functional and liable to experience HTN [35]. Contrary to the findings, interestingly, in our patient cohort, eight patients were on anti-HTNs at the time of recruitment for ²²⁵Ac-DOTATATE TAT, and five among them belonged to the H&NPGL category. Generally, in our clinical setting, asymptomatic H&NPGLs are closely followed up with a “wait and watch” policy, and only symptomatic patients are referred for PRRT. This appears to be the probable explanation for the high percentage of H&NPGL patients with hypertension. From this standpoint, the effectiveness of ²²⁵Ac-DOTATATE TAT goes beyond the response as compared to ¹⁷⁷Lu-PRRT with an effective control of HTN in all H&NPGLs and complete discontinuation of anti-HTNs in two patients.

Among the three patients with sympathetic PGLs, it is interesting to note that two did not benefit from ¹⁷⁷Lu-PRRT and faced uncontrolled HTN. After treatment with ²²⁵Ac-DOTATATE TAT, one patient clinically responded, but one patient with a lung mass experienced cardiac arrest and subsequently died. The patient also has shown the progression

Table 7 Comparison of pre- and post-therapy laboratory parameters

Laboratory parameters	Baseline (median, IQR)	Post-therapy (median, IQR)	P-value
Hematotoxicity			
Hemoglobin g/dL	10.5 (9.9–11.8)	10 (10.3–11.5)	0.4316
*Platelets 100,000/mm ³	242 ± 92.4 (125–411)	247 ± 81 (135–348)	0.8061
*Leukocytes cells/mm ³	6358 ± 2420 (3730–10,600)	6068 ± 2202 (2900–9110)	0.6881
Nephrotoxicity			
*Blood urea, mg/dL	28.04 ± 9 (16.2–44.7)	24.7 ± 7 (14–36)	0.3335
Serum creatinine mg/dL	0.88 (0.8–0.97)	0.93 (0.91–0.98)	0.3594
Hepatotoxicity			
*Serum bilirubin, mg/dL	0.52 ± 0.2 (0.27–0.85)	0.42 ± 0.11 (0.26–0.58)	0.1945
ALP	129.4 (107–177)	109 (93–172)	0.0117
SGOT	25.2 (20.7–33)	27 (24–41)	0.3008
SGPT	26.5 (16–39)	26.5 (18–32)	0.7422

SD, standard deviation; IQR, interquartile range; ALP, alkaline phosphatase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

*All parameters are shown as mean ± standard deviation and range

of the lung mass after two cycles of ^{225}Ac -DOTATATE TAT and might have experienced catecholamine hypersecretion followed by cardiac tamponade.

At the time of analysis, two patients had achieved up to a cumulative activity of >70 MBq of ^{225}Ac -DOTATATE and completed the treatment regimen with partial response status at the last imaging assessment and more importantly have shown sustained response. Both patients are on active follow-up with no reported adverse events. Five patients are actively undergoing treatment.

No events of myelodysplastic syndrome or grade III myelosuppression were noted. One inherent drawback of alpha therapy is the lack of dosimetry techniques. However, our short-term follow-up data revealed no grade III/IV toxicities even at higher cumulative doses of >37 MBq. The low-grade toxicities experienced in the patient population demonstrate two things: firstly, even higher doses of ^{225}Ac -DOTATATE up to ~ 74 MBq are safe. Secondly, despite receiving a median tolerable cumulative activity of 34.5 GBq (932.4 mCi) of ^{177}Lu -PRRT in seven patients, an additional treatment regimen with ^{225}Ac -DOTATATE TAT was also safe.

In accordance with our results, the long-term results of ^{225}Ac -DOTATATE in GEP-NETs reported by Bal et al. [27] revealed cumulative doses of up to 111 MBq were well tolerated with minimal adverse events. Another study by Kratochwil et al. [36] reported cumulative doses of even 80 MBq safe in patients with advanced-stage malignancies. However, extensive research with consistent follow-up intervals over the long term must be carried out to deduce any conclusions and achieve better safety results.

This study has recognized certain limitations. The sample size is small; nevertheless, to the best of our knowledge, this is the first study to give an overview of the role of ^{225}Ac -DOTATATE therapy in PGL. Secondly, the short follow-up duration is another drawback. In an indolent cancer like PGL with a slow rate of progression, a longer follow-up duration is required. Thirdly, due to the COVID-19 pandemic conditions, the follow-up of the patients and the response evaluation scan time-points were inconsistent and hence were acquired either after 2 or 3 cycles of treatment. Fourthly, non-contrast CT was conducted in all patients. Kidney toxicity was only followed by creatinine levels, but no renal scans were acquired. The current study with a small number of patients and only one event of disease progression did not justify conducting survival and other multiparametric analysis. Finally, biochemical tumor response was not analyzed as an endpoint in the study for the following reasons: Majority ($n=7/9$) patients had a normal level of Chromogranin A in the blood at the baseline, and other tumor markers including metanephrines and catecholamines were not consistently evaluated in all the patients, but in this study, we assessed

patients with morphological response which is considered superior to the biochemical response.

The pilot results are encouraging and demonstrate ^{225}Ac -DOTATATE therapy as an effective and safe option in the treatment of metastatic PGLs. In addition, the initial results suggest ^{225}Ac -DOTATATE therapy as a salvage treatment option in patients refractory to ^{177}Lu -PRRT. Our study provides a framework for a new promising aspect of treatment of advanced-stage PGLs. Moreover, the preliminary results of this pilot study provide a blueprint and encourage to conduct future prospective, two-armed randomized control studies on the head-to-head comparison between beta-particle-based ^{177}Lu -DOTATATE and alpha-particle-based ^{225}Ac -DOTATATE treatment in PGLs.

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Data availability The data are available for transparency purposes.

Declarations

Ethics approval Ethical clearance received Ref. No IEC-517.

Consent to participate Informed consent was obtained from all patients.

Conflict of interest The authors declare no competing interests.

Disclaimer This work has not been submitted elsewhere as a full article or is not under consideration to any other journal.

References

- Lloyd RV, Osamura RY, Klöppel G & Rosai J. WHO classification of tumours of endocrine organs. 2018.
- VL Martucci K Pacak 2014 Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment *Curr Probl Cancer* 38 7 41 <https://doi.org/10.1016/j.cupr.2014.01.001>
- RE Lieberman JR Adler SG Soltys C Choi IC Gibbs SD Chang 2012 Stereotactic radiosurgery as the primary treatment for new and recurrent paragangliomas: is open surgical resection still the treatment of choice? *World Neurosurg* 77 745 761 <https://doi.org/10.1016/j.wneu.2011.03.026>
- C Suárez JP Rodrigo CC Bödeker 2013 Jugular and vagal paragangliomas: systematic study of management with surgery and radiotherapy *Head Neck* 35 8 1195 1204 <https://doi.org/10.1002/hed.22976>
- C Suárez JP Rodrigo WM Mendenhall 2014 Carotid body paragangliomas: a systematic study on management with surgery and radiotherapy *Eur Arch Otorhinolaryngol* 271 23 34 <https://doi.org/10.1007/s00405-013-2384-5>

6. C Capatina G Ntali N Karavitaki AB Grossman 2013 The management of head-and-neck paragangliomas *EndocrRelat Cancer* 20 R291 R305 <https://doi.org/10.1530/ERC-13-0223>
7. Pacak K, Tella SH. Pheochromocytoma and Paraganglioma. [Updated 2018 Jan 4]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK481899/>.
8. S Hescot S Leboulleux L Amar D Vezzosi I Borget C Bournaud-Salinas 2013 One-year progression-free survival of therapy-naive patients with malignant pheochromocytoma and paraganglioma *J Clin Endocrinol Metab* 98 4006 4012 <https://doi.org/10.1210/jc.2013-1907>
9. Huang H, Abraham J, Hung E, Steven Averbuch, Maria Merino, Seth M Steinberg, et al. Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. *Cancer*. 2008;113:2020–28. <https://doi.org/10.1002/cncr.23812>.
10. C Jimenez E Rohren MA Habra T Rich P Jimenez M Ayala-Ramirez 2013 Current and future treatments for malignant pheochromocytoma and sympathetic paraganglioma *Curr Oncol Rep* 15 356 371 <https://doi.org/10.1007/s11912-013-0320-x>
11. E Baudin MA Habra F Deschamps G Cote F Dumont M Cabanillas 2014 Therapy of endocrine disease: treatment of malignant pheochromocytoma and paraganglioma *Eur J Endocrinol* 171 R111 R122 <https://doi.org/10.1530/EJE-14-0113>
12. D Taïeb A Kaliski CC Boedeker V Martucci T Fojo JR Adler Jr K Pacak 2014 Oct Current approaches and recent developments in the management of head and neck paragangliomas *Endocr Rev* 35 5 795 819 <https://doi.org/10.1210/er.2014-1026>
13. S Nörling M Ullrich J Pietzsch CG Ziegler G Eisenhofer A Grossman 2019 Current management of pheochromocytoma/paraganglioma: a guide for the practicing clinician in the era of precision medicine *Cancers (Basel)* 11 1505 <https://doi.org/10.3390/cancers11101505>
14. S Gonias R Goldsby KK Matthay R Hawkins D Price J Huberty 2009 Phase II study of high-dose [¹³¹I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma *J Clin Oncol* 27 4162 4168 <https://doi.org/10.1200/JCO.2008.21.3496>
15. DA Pryma BB Chin RB Noto JS Dillon S Perkins L Solnes 2019 Efficacy and safety of high-specific-activity ¹³¹I-MIBG therapy in patients with advanced pheochromocytoma or paraganglioma *J Nucl Med* 60 623 630 <https://doi.org/10.2967/jnumed.118.217463>
16. J Strosberg G El-Haddad E Wolin A Hendifar J Yao B Chasen 2017 NETTER-1 Trial Investigators. Phase 3 trial of ¹⁷⁷Lu-DOTATATE for midgut neuroendocrine tumours *N Engl J Med*. 376 125 35
17. MP Yadav S Ballal C Bal 2019 Concomitant ¹⁷⁷Lu-DOTATATE and capecitabine therapy in malignant paragangliomas *EJNMMI Res* 9 13
18. K Nastos VTF Cheung C Toumpanakis S Navalkisoor AM Quigley M Caplin 2017 Peptide receptor radionuclide treatment and (¹³¹I)-MIBG in the management of patients with metastatic/progressive pheochromocytomas and paragangliomas *J Surg Oncol* 115 425 434 <https://doi.org/10.1002/jso.24553>
19. G Kong S Grozinsky-Glasberg MS Hofman J Callahan A Meirovitz O Maimon 2017 Efficacy of peptide receptor radionuclide therapy for functional metastatic paraganglioma and pheochromocytoma *J Clin Endocrinol Metab* 102 3278 3287
20. A Imhof P Brunner N Marincek M Briel C Schindler H Rasch 2011 Response, survival, and long-term toxicity after therapy with the radiolabelled somatostatin analogue [⁹⁰Y-DOTA]-TOC in metastasised neuroendocrine cancers *J Clin Oncol* 29 2416 2423
21. S Severi A Bongiovanni M Ferrara S Nicolini F Mauro Di M Sansovini 2021 Peptide receptor radionuclide therapy in patients with metastatic progressive pheochromocytoma and paraganglioma: long-term toxicity, efficacy and prognostic biomarker data of phase II clinical trials *ESMO Open*. 14 6 100171
22. Baum RP, Zhang J, Schuchardt C, Mueller D, Maecke H. First-in-human study of novel SSTR antagonist ¹⁷⁷Lu-DOTA-LM3 for peptide receptor radionuclide therapy in patients with metastatic neuroendocrine neoplasms: dosimetry, safety and efficacy. *J Nucl Med*. 2021;5:jnumed.120.258889 <https://doi.org/10.2967/jnumed.120.258889>
23. C Kratochwil FL Giesel F Bruchertseifer W Mier C Apostolidis R Boll 2014 ²¹³Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience *Eur J Nucl Med Mol Imaging* 41 2106 2119
24. S Ballal MP Yadav C Bal RK Sahoo M Tripathi 2020 Broadening horizons with ²²⁵Ac-DOTATATE targeted alpha therapy for gastroenteropancreatic neuroendocrine tumour patients stable or refractory to ¹⁷⁷Lu-DOTATATE PRRT: first clinical experience on the efficacy and safety *Eur J Nucl Med Mol Imaging* 47 934 946
25. Delpassand E, Tworowska I, Torgue J, Shanoon F, Hurt J, Ranganathan D et al. First-in-human dose escalation of AlphaMedix™ for targeted alpha-emitter therapy of NETs. *Journal of Nuclear Medicine* May 2020, 61 (supplement 1) 41.
26. Yadav MP, Ballal S, Sahoo RK, Tripathi M, Seth A, Bal C. Efficacy and safety of ²²⁵Ac-PSMA-617 targeted alpha therapy in metastatic castration-resistant prostate cancer patients. *Theranostics*. 2020; 10:9364–77. doi:<https://doi.org/10.7150/thno.48107>. Available from <https://www.thno.org/v10p9364.htm>.
27. CS Bal S Ballal MP Yadav 2021 Long-term outcome of ²²⁵Ac-DOTATATE targeted alpha therapy in patients with metastatic gastroenteropancreatic neuroendocrine tumors *J Nucl Med* 62 supplement 1 19
28. RL Wahl H Jacene Y Kasamon MA Lodge 2009 From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumours *J Nucl Med* 50 Suppl 1 122S S150
29. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Publish Date: November 27, 2017.
30. Fayers PM, Aaronson NK, Bjordal K, On behalf of the EORTC Quality of Life Group, et al. The EORTC QLQ-C30 scoring manual (3rd edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
31. MT King 1996 The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30 *Qual Life Res* 5 555 567
32. K Bjordal E Hammerlid M Ahlner-Elmqvist A Graeff de M Boysen JF Evensen 1999 Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35 *J Clin Oncol* 17 1008 1019
33. S Satapathy BR Mittal A Bhansali 2019 Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: a systematic review and meta-analysis *Clin Endocrinol (Oxf)* 91 718 727
34. MD Williams 2017 Paragangliomas of the head and neck: an overview from diagnosis to genetics *Head Neck Pathol* 11 278 287
35. TY Colen FG Mihm TP Mason JB Roberson 2009 Catecholamine-secreting paragangliomas: recent progress in diagnosis and perioperative management *Skull Base* 19 377 385

36. Kratochwil, C., Apostolidis, L., Rathke, H., Apostolidis C, Bicu F, Bruchertseifer F, et al. Dosing ^{225}Ac -DOTATOC in patients with somatostatin-receptor-positive solid tumors: 5-year follow-up of hematological and renal toxicity. *Eur J Nucl Med Mol Imaging* (2021). <https://doi.org/10.1007/s00259-021-05474-1>.

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