 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) WITH ^{177}LU-DOTATATE IN METASTATIC PHAEOCHROMOCYTOMAS AND PARAGANGLIOMAS – A SINGLE CENTRE RETROSPECTIVE ANALYSIS OF EXPERIENCE AT AN *ENETS CENTRE OF EXCELLENCE*

Title: ^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) in Metastatic phaeochromocytomas and paragangliomas (mPPGL) – A single centre retrospective analysis of experience at an ENETS *Centre of Excellence*

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 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

Data Availability statement:

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Funding statement:

No funding was obtained for this study.

Conflict of interest:

The authors have no relevant conflicts of interest to declare.

Ethical approval statement: As this study was retrospective audit of practice, ethical approval was not required under the UK Policy Framework for Health and Social Care Practice. Audit registration number: RFH_23/24678.

Word counts:

Manuscript (excluding abstract and references): 5456

ABSTRACT:

Introduction: ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) represents a possible therapeutic option for patients with metastatic inoperable phaeochromocytomas (PCC) and paragangliomas (PGL) who demonstrate adequate somatostatin analogue binding on molecular imaging. We describe treatment outcomes in our cohort of patients stratified according to germline pathogenic variants (PV) in Succinate Dehydrogenase (*SDHx*) subunit-encoding genes.

Methods: In this retrospective analysis, we evaluated 20 patients with metastatic PCC/PGL who underwent two or more cycles of ^{177}Lu-DOTATATE therapy. Clinical, radiological, and biochemical responses were assessed 8-12 weeks after the final PRRT cycle. We describe overall treatment efficacy at follow-up after stratifying according to the presence of germline *SDHx* PV. Radiological progression was quantified based on the sum of the longest diameter (SLD) of the target lesion. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier survival analysis. We also aimed to investigate the impact of PRRT on health-related quality of life (HRQoL), as assessed using the EORTC QLQ-GINET21 questionnaire.

Results: After a median follow-up of 29 months, we confirmed stable disease in 12 patients (60%), a partial response in one (5%), and progressive disease in 7 patients (35%). The absolute mean difference in SLD was +5±12 mm for bone lesions, -4±6 mm for peritoneal, +8±14mm for liver lesions and -1± 5 mm for lymph nodes (paired t-test p-value 0.273, 0.741, 0.208 and 0.826, respectively). Thirteen patients (65%) had received two or more previous lines of treatment. The overall median PFS for the entire cohort, PGL patients, *SDHx* positive and negative groups, was 24 months (95% CI, 9.9-38.1), 18 months (95% CI, 8.4-27.6), 24 months (95% CI, 11.9-36.0) and 18 months (95% CI, 0-48) respectively. No grade 3/4 cytopenia or

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nephrotoxicity was observed. Overall, HRQoL improved after PRRT, as evidenced by the progressive decline in overall symptom scores in the QLQ-GINET21.

Conclusion: ^{177}Lu-PRRT appears to be an effective therapy with a good safety profile for patients with metastatic PPGL. It also appears to improve HRQoL in patients with metastatic PPGL. Further studies are needed to explore the most effective treatment modalities in this group of patients and their sequencing.

Keywords: Phaeochromocytomas, Paraganglioma, ^{177}Lu-DOTATATE, Peptide receptor radionuclide treatment, Health related quality of life

1. INTRODUCTION:

Phaeochromocytomas (PCC) and paragangliomas (PGL), collectively referred to as PPGL, are rare tumours that originate from neural crest cells and have the potential to become metastatic [1]. The prevalence of metastases ranges from 2.4% to 50% for PGL and 2% to 13% for PCC [2]. PCCs arise from the adrenal medulla, while PGLs typically originate from extra-medullary sites, such as the head & neck, chest, abdomen and pelvis [1]. PPGL represents a significant category of hereditary neoplasms, with up to 40% of cases stemming from identifiable germ-line pathogenic variants (PV) [1]. Approximately 70% of all patients with inherited PPGL can be categorised into three clusters based on their molecular characteristics and germline PV in susceptibility genes. Cluster 1A tumours commonly exhibit PVs in the Krebs cycle and *SDHx* genes, while Cluster 1B tumours involve PVs in the hypoxia-signalling and *Von Hippel-Lindau* pathways (*VHL)* [3]. They are characterised by increased aggressiveness and a relatively higher risk of metastasis [3]. In contrast, cluster 2 tumours are associated with pathogenic variants in tyrosine kinase-linked signalling pathways (e.g. *RET*, *NF1*) and tend to display less aggressive behaviour [3]. Tumours in the rare cluster 3 are primarily associated with *Wnt* signalling pathway involvement and exhibit aggressive and metastatic behaviour [3].

Although cytoreductive surgical resection of the primary tumour is the treatment of choice for metastatic PPGL (mPPGL), this can be challenging due to various factors [3,4]. Inoperable mPPGL are usually offered alternative therapeutic modalities, such as chemotherapy, external beam radiotherapy, tyrosine kinase inhibitors, radiofrequency ablation, and/or radionuclide therapy [3–5]. The response rate and progression free survival (PFS) of systemic therapy for mPPGL varies depending on factors such as the genetic PV, somatostatin receptor (SSTR) expression, disease extent, and the type of treatment employed. Chemotherapy with

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cyclophosphamide, vincristine and dacarbazine (CVD) shows a partial response rate of 37% and a PFS of 20 months for PCC and 40 months for PGL, while the response rate of systemic therapy with sunitinib, a tyrosine kinase inhibitor, demonstrated a disease control rate of 57% and a PFS of 4.1 months [6].

In recent years, targeted radiotherapies have emerged as a viable treatment option for patients with mPPGL [7]. Radiolabelled meta-iodo-benzyl-guanidine (^{131}I-MIBG) therapy targets the norepinephrine/noradrenaline (NE) transporter where the theranostic pair (^{123}I-MIBG for imaging and ^{131}I-MIBG for therapy) binds and is internalised via the NE transporter and is transported intracellularly to secretory granules [7]. While ^{131}I-MIBG therapy has been reported to have a disease control rate (DCR) up to 85%, it carries significant risk of haematological toxicity (up to 87%) and myelodysplastic syndrome (4%)[8–10]. Peptide receptor radionuclide therapy (PRRT) targets tumours expressing somatostatin receptors (SSTR) not only in gastro-enteropancreatic neuroendocrine neoplasms (GEP NEN), but also in bronchial NENs, NENs of unknown primary, and PPGL [11]. It has been approved for the regulatory use for grade 1 or 2 GEP-NENs after the successful outcomes of the NETTER-1 trial [12]. Evidence has also been emerging for the effectiveness of PRRT therapy in mPPGL, notably in patients with cluster 1A-related PPGL tumours, such as PV in *SDHx*, which demonstrate a high expression of SSTR, suggesting that targeted molecular therapies tailored to these receptors could be particularly effective in treating these tumours [5,13]; however, there are few published data regarding the effectiveness of PRRT in mPPGL [14].

In the present study, we have retrospectively analysed our data from patients with inoperable or progressive mPPGL who received PRRT therapy at an *ENETS Centre of Excellence* at the Royal Free Hospital in London, UK. Our objectives were to document the effectiveness and safety of PRRT in mPPGL, to gather further evidence of efficacy, to explore the effects on

health-related quality of life (HRQoL), and to understand the interaction of germline PV in the genes encoding the subunits for succinate dehydrogenase (*SDHx*) with treatment response.

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2. MATERIALS AND METHODS:

2.1 Population:

In this study, we retrospectively examined patients with mPPGL who underwent treatment with ^{177}Lutetium-tetra-azacyclododecane tetra-acetic acid octreotate (^{177}Lu-DOTATATE) between 2013 and 2023 at the ENETS *Centre of Excellence* based at the Royal Free London NHS Foundation Trust, London, UK. For this study, we selected all patients with a previous diagnosis of mPPGL. The original diagnosis was determined based on various factors, including symptomatology, biochemistry, histology, and imaging modalities, including ^{123}I-MIBG scintigraphy, ^{111}In-diethylenetriamine-pentaacetic acid (DTPA)-Octreotide or ^{68}Ga-DOTATATE Positron Emission Tomography (PET)/Computed Tomography (CT), and ^{18}F-DG PET (fluoro-deoxyglucose Positron Emission Tomography), Contrast-enhanced CT (CECT) and Magnetic Resonance Imaging (MRI). Patients were classified as metastatic if metastases were present at diagnosis (synchronous) or during follow-up after initial surgery (metachronous).

Treatment with PRRT was offered following multidisciplinary review of each case. The treatment with PRRT was offered to patients with either inoperable metastatic but radiologically avid lesions on ^{68}Ga-DOTATATE scans at the time of the original diagnosis, or to those with evidence of disease progression during follow-up after first-line treatment. All patients offered treatment had documented tumour avidity on ^{68}Ga-DOTATATE PET/CT at known sites of disease at least equal to or greater than background liver uptake (Krenning score ≥2). Though ^{18}FDG-PET scans were not routinely done prior to PRRT, when there were concerns or the possibility of discordant disease, ^{18}FDG-PET scans were performed and, if patients were found to have discordant ^{68}Ga-DOTATATE and ^{18}FDG disease, PRRT was withheld. When required, patients with symptomatically controlled and surgically-treatable

primary or metastatic disease, as well as patients with significant bone marrow disease (white blood cell count of less than or equal to 2×10^9/l; and a platelet count of less than 70×10^9/l) or renal failure [glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m^2], advanced heart failure, or a *World Health Organization (*WHO) performance status of 3 or 4, were not considered eligible for treatment.

For the purpose of this study, we documented information on patient demographics, including age, sex, tumour type, the presence and extent of metastases, functionality of the tumour, operability, genetic background, and *Radiological Evaluation Criteria in Solid Tumour* (RECIST) 1.1 assessment pre-PRRT therapy[15].

As this project was a retrospective audit of practice and registered with the hospital audit department (audit registration reference number: RFH_23/24678), ethical approval was not required under the UK Policy Framework for Health and Social Care Practice.

2.2 Genetic testing:

Genetic testing and sequencing were performed at *Exeter Genomics Laboratory*, in Exeter, UK. The coding regions and exon/intron boundaries of the dihydrolipoamide S-succinyltransferase (*DLST*), fumarate hydratase (*FH*), MYC-associated factor X (*MAX*), malate dehydrogenase-2 (*MDH2*), multiple endocrine neoplasia-1 (*MEN1*), succinate dehydrogenase-A (*SDHA*), succinate dehydrogenase-AF2 (*SDHAF2*), succinate dehydrogenase-B (*SDHB*), succinate dehydrogenase-C (*SDHC*), succinate dehydrogenase-D (*SDHD*), solute carrier gene 25A11 (*SLC25A11*), transmembrane protein 127 (*TMEM127*) and Von-Hippel-Lindau (*VHL*) genes, and exons 5, 7, 8, 10, 11, 13, 14, 15, 16 of the rearranged during transfection (*RET*) gene, were analysed by targeted next-generation sequencing (Twist Core Human Exome/Illumina NextSeq). Identified variants were classified according to standards and guidelines of the

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American College of Medical Genetics and Genomics and the *Association for Molecular Pathology* (ACMG-AMP) [16].

2.3 PRRT therapy administration protocol:

As per our local protocol, prior to administering PRRT therapy, imaging scans were reviewed to confirm uptake on ^{68}Ga-DOTATATE PET/CT at known sites of disease at least equal to or greater than background liver (Krenning score ≥2). The treatment was carried out in a protected isolation room located in the oncology unit at Royal Free Hospital. Prior to the administration of ^{177}Lu-DOTATATE, oral anti-emetic medication (ondansetron 4 mg) was administered. Renal protection was implemented using standard amino-acid infusion (2.5% lysine and 2.5% arginine in 1 L of 0.9% NaCl: infusion of 250 ml/h) infused over a period of 4 hours, started 30 minutes before the administration of the radiopharmaceutical via a secondary pump system. Gelofusine 500 ml over 3 hours prior to PRRT therapy was given to patients whose eGFR was between 30 and 60 mmol/L. The administered tracer activity of ^{177}Lu-DOTATATE was 6.9 to 7.9 GBq, except for one patient with mild thrombocytopenia (baseline platelet count of 87 × 10^9/l) who received a reduced tracer activity of ^{177}Lu-DOTATATE (3.7 GBq). Blood pressure was monitored regularly during administration of PRRT therapy. All patients underwent a ^{177}Lu-DOTATATE post-therapy uptake scan at 4 hours after administration of PRRT therapy. According to the standard treatment protocol, this involved administering 3-4 cycles of therapy with 10-12 weeks intervals between each treatment. In the event of significant toxicity, fewer cycles were given, as noted below.

2.4 Follow-up and assessment of treatment efficacy:

Patients' symptoms and adverse effects were evaluated after each cycle and three months after the final cycle of PRRT therapy. Routine blood tests, including haematology, liver, renal, thyroid function tests, as well as tumour markers e.g. plasma free metanephrines (PFMN) and

plasma free normetanephrines (PFNMN), were compared before and after therapy. Elevated PFMN and PFNMN were defined as >3 times of the contemporaneous upper reference limit. The follow-up was terminated only if the patient died or received palliative care, in which case only information regarding the patient's final status was recorded. Restaging cross-sectional imaging (CECT or MRI) was performed between 6 and 12 weeks after the last dose of PRRT therapy, and subsequently every 4-6 months until November 2024, or death, to assess disease activity and determine if the disease remained stable or had progressed. The scans were reviewed by experienced radiologists. Routine restaging ^{68}Ga-DOTATATE PET/CT scans were not performed unless there were concerns of disease progression on cross-sectional imaging. In those circumstances, cases were discussed in MDT meetings, and appropriate investigation, and treatment plans were made.

The efficacy of the treatment was assessed based on clinical, radiological, and biochemical evaluations. The clinical assessment involved assessing catecholaminergic features and changes in anti-hypertensive medications. Radiological evaluation included CECT, MRI and were evaluated using RECIST 1.1 criteria[15]. Biochemical evaluation was based on PFMN and PFNMN levels, which were compared before the commencement of PRRT and after the final dose of PRRT.

Anatomical imaging involved the use of one of following imaging modalities: CECT, MRI, or the CT component of ^{68}Ga-DOTATATE-PET/CT scans only if it was found to be of adequate diagnostic quality [17], and the CECT/MRI responses were evaluated using RECIST version 1.1. The visual and/or semi-quantitative analysis based on molecular imaging or other quantitative measurement parameters such as Maximum Standardized Uptake Value (SUVmax), Standardized Uptake Value normalised to Lean Body Mass (SUL) were not used or calculated to assess treatment response. *Complete response (CR)* was defined as the disappearance of all target lesions, *Partial Response (PR)* as at least a 30% decrease in the sum

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of the longest diameters (SLD) of target lesions (relative to baseline sum) with no new lesions or progression of non-target lesions, and *Progressive Disease (PD)* as a more than 20% increase in SLD with an absolute increase more than 5mm, or appearance of new lesion or non-target progress as at least 20% increase (≥5 mm absolute increase) in the SLD of target lesions (relative to the smallest sum) or appearance of new lesions [15,18]. Disease control rate (DCR) was calculated by combining stable disease rate, partial response rate and complete response rate.

Overall survival (OS) was calculated for all patients and was defined as the interval between the first cycle of PRRT and death. Progression-free survival (PFS) was defined as the interval between the date of first cycle of PRRT and the date of first radiological progression according to RECIST criteria or disease-related death.

2.5 Health-related quality of life (HRQoL):

To assess the impact of PRRT on HRQoL, the EORTC NET-specific questionnaire QLQ-GINET21 was utilised (Supplementary figure 1). The questionnaire was completed by patients at baseline and following each cycle of PRRT, on the day of their subsequent cycle. The QLQ-GINET21 comprises a total of 21 items, 17 of which are multi-item scales distributed across five domains: endocrine symptoms (ED), gastrointestinal symptoms (GI), treatment-related symptoms (TR), disease-related worries (DRW), and social functioning (SF21). The remaining four single items relate to body image (BI), information (INF), sexual functioning (SF), and muscle and/or bone pain (MBP). Response options on the Likert scale ranged from 1 (“not at all”) to 4 (“very much”), with four of the items also including a “not applicable” option.

2.6 Treatment toxicity:

Minor side effects according to *Common Terminology Criteria for Adverse Events* (CTCAE) v5 during and after therapy were recorded with telephone calls after 2-4 weeks of each cycle of PRRT. Significant side-effects of treatment, in terms of renal and haematological toxicity, were collated and graded according to CTCAE v5[19].

2.7 Statistical analysis:

Statistical analysis was performed using SPSS (version 23, IBM). Categorical variables were expressed in absolute numbers and percentages (%). Continuous variables were expressed as mean value ± standard deviation (SD).

We compared the difference in baseline and follow-up clinical, biochemical, and radiological characteristics following PRRT treatment, for the total group of patients as well as after stratification for *SDHx*-PV. For this purpose, we used a non-parametric test since some data were missing, especially biochemical analysis, and they were not normally distributed. Differences between the *SDHx* positive and negative groups were assessed using chi-square test for qualitative data and the unpaired t-test and/or the non-parametric Man-Whitney U test for quantitative data. We have also estimated post-treatment differences in the sum of the longest diameter (SLD) of the target metastatic lesions, focusing on the most commonly observed metastatic locations.

For the purpose of survival analysis, PFS and OS were estimated for the entire study cohort and according to the carrier status for PV in *SDHx* using the Kaplan-Meier method. The log-rank test was used the compared the PFS in the *SDHx* PV-stratified groups. A p-value <0.05 was considered statistically significant.

For the HRQoL analysis, a descriptive approach was employed due to the limited size and distribution of the dataset. Raw questionnaire scores for each visit were standardised using a

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linear transformation to a scale ranging from 0 to 100 following the EORTC linear transformation equation. On this scale, higher values correspond to more severe or worsened symptoms [20]. Incomplete responses were excluded from the analysis.

3. RESULTS:

Between 2013 and 2023, a comprehensive cohort of 166 patients with PCC/PGL underwent follow-up at Royal Free Hospital in London. Of these patients, 21 individuals with inoperable or progressive metastatic PCC/PGL received treatment with ^{177}Lu-PRRT. However, one patient was excluded from the study due to the concurrent administration of other treatments, resulting in a final inclusion of 20 patients in the analysis. Figure 1 depicts the flowchart of patient selection for the purpose of this study. Of the 20 patients included in the study, 3 patients (PCC:1, PGL:2) were offered PRRT immediately after index presentation with a diagnosis of inoperable metastatic disease based on radiologically-avid lesions on ^{68}Ga-DOTATATE scans and discussion at the NET MDT.

Demographics

Of the 20 patients, four had a diagnosis of PCC and 16 had PGL. The sample consisted of 11 male patients (55%) and 9 female patients (45%) with a mean ± SD age of 58±14 years at the start of PRRT. Of the total cohort, 11 patients (55%) had a germline *SDHx* PV (PCC: 1 [*SDH-B*], PGL: 10 [*SDH-B*:8, *SDH-B* and *D*: 1, *SDH-C*:1]), while a PV was not found in 6 patients (PCC: 3, PGL: 3; 30%). Three patients (PGL:3) did not have genetic analysis. At baseline, 8 patients (40%) had elevated PFNMN, while 5 patients (25%) had normal PFNMN levels. Baseline PFNMN levels were not available for 7 patients. The indication for PRRT was radiological progression of disease in 17 patients (85%) or inoperable disease with metastases at the time of diagnoses in 3 patients (15%). The median number of PRRT cycles administered was 4 with a mean cumulative dose of 24.55 ± 7.77 GBq. The median duration of follow-up from the start of PRRT was 29 months (range 5-134 months). Of the 20 patients, 17 patients had previous treatment for mPPGL. These treatments included resection of primary tumour (n:

 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

17, 85%), SSTAs (n:6, 30%), MIBG therapy (n: 3, 15%), Chemotherapy (n: 4, 20%), molecular targeted therapy (n: 2, 10%), radiotherapy (n: 4, 20%), ^{90}Yttrium Octreotate therapy (n: 1, 5%). Around half of the patients (n:9, 45%) had received previous 2 lines of other treatment, followed by 5 patients (25%) had received one line of previous treatment. A summary of the patient demographics and tumour characteristics is shown in Table 1. The full analysis of patients' demographics is provided as Supplemental Table 1.

Radiological responses to treatment

Of the total cohort, there were no complete responses noted following PRRT; one patient showed a partial response (5%), SD was confirmed in 12 patients (60%), while PD was recorded in 7 patients (35%). Of the cohort of patients with PD at baseline (n:17), one patient showed a partial response (6%), SD was confirmed in 9 (53%), and 7 patients (41%) exhibited PD. The most common site of metastases at the start of PRRT was bone in 12 (63%), followed by lymph nodes in 6 (32%) and the peritoneum in 6 (32%). The mean SLD at baseline was 101 ± 59 mm, while the mean SLD at follow-up was 108 ± 66 mm (non-significant). Of the 20 patients, 7 (37%) developed new lesions on follow-up imaging. Radiological evaluation using RECIST assessment in the study cohort is described in Table 2. Detailed assessment including the site of metastases and RECIST assessment of the total cohort is provided in Supplemental Table 2.

We have also compared the changes in terms of the sum of the longest diameter of target lesions, focusing on metastatic disease. Focusing on the sites of the mostly prevalent metastatic disease, we observed the following changes, which are also shown in Figure 4:

- For bone lesions the mean SLD was 23 ± 10 mm at baseline versus 28 ± 18 mm at follow up (absolute mean difference, +5 ±12 mm, p-value for paired sample, 0.273). With regards

to the treatment effect on bone lesions, a documented increase in size of bone lesions (>5 mm compared to baseline) was evident in 5 patients, a reduction in size (more than 30% reduction from baseline) was evident in one patient, and remained stable in 5 cases.

- For peritoneal lesions the mean SLD was 42 ± 22 mm at baseline and 39 ± 20 mm at follow-up (absolute mean difference, -4 ± 6 mm, p-value for paired sample 0.741). With regards to the treatment effect on peritoneal lesions, 3 patients had a reduction in the size of the peritoneal lesions (>5mm reduction compared to baseline) while 2 patients had stable peritoneal lesions post-PRRT.
- For liver lesions, the mean SLD was 23 ± 10 mm versus 32 ± 18 mm at follow-up (absolute mean difference, +8 ± 14 mm, p-value for paired samples, 0.208). With regards to the treatment effect on liver lesions, 3 patients showed disease progression (>30% increase in SLD compared to baseline) and 2 had stable liver lesions.
- For metastases to lymph nodes, the mean SLD was 25 ± 10 mm versus 24 ± 10 mm at follow-up (absolute mean difference -1 mm ± 5 mm, p value for paired sample 0.826). With regards to the treatment effect on lymph node size, 4 patients had stable size post-PRRT, whereas one patient had >30% reduction in size of lymph node and 2 patients had >5mm increase in the size of the lymph nodes.

Anti-hypertensive treatment

Of the entire cohort, 12 (60%) patients were on treatment with anti-hypertensives e.g., β-adrenoceptor blockers, α-adrenoceptor blockers, angiotensin-converting enzyme inhibitors and/or calcium channel blocker prior to their treatment with ^{177}Lu-PRRT. Of the 8 patients with elevated PFNMN at baseline, anti-hypertensive doses remained unchanged after the completion of treatment in 5 patients (62.5%), an increased number of medications was

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required in 2 patients (25%), while a temporary increase in the dose of medications was needed in the case of one patient (12.5%).

Toxicity

No new CTCAE grade 3/4 cytopenia nor nephrotoxicity was seen. Two patients (10%) developed anaemia (CTCAE grade 1), while 2 patients (10%) developed thrombocytopenia (CTCAE grade 2). One patient received 2 cycles of half-standard dose (3.7 GBq) of PRRT due to baseline thrombocytopenia (baseline platelet counts of 87×10^9/l) but received no further doses of PRRT therapy due to concern regarding ongoing and persistent thrombocytopenia (platelet counts 65×10^9/l to 80×10^9/l). Five patients (25%) experienced fatigue (CTCAE Grade 1) and 4 patients (20%) experienced bone pain (CTCAE Grade 1-2), 2 patients (10%) experienced nausea (CTCAE Grade 1) and one patient (5%) had hiccoughs post-PRRT therapy. All side-effects were transient. A summary of the side-effects and changes in anti-hypertensives pre and post PRRT is shown in Table 3 and Supplemental Table 3.

Survival analysis

Figure 2 shows Kaplan Meier plots for PFS. Of the total cohort, median PFS from the start of PRRT therapy was 24 months (95% CI, 9.9-38.1). The median PFS for PGL was 18 months (95% CI, 8.4-27.6). OS for the total study cohort and median PFS for PCC was not reached.

Of the total cohort of patients, 11 patients (55%) were identified as carriers of *SDHx* PV, whereas 6 patients (32%) were not. Within the *SDHx* PV-positive subgroup, 60% of patients demonstrated either stable or a partial response to PRRT, whereas in the *SDHx* PV-negative group, 66% of patients experienced stable disease or a partial response to PRRT. The median

PFS for those in the *SDHx* PV-positive group was calculated to be 24 months (95% CI, 11.9-36.0), while for those in the *SDHx* PV-negative group, was calculated to be 18 months (95% CI, 0-48). Figure 3 depicts a comparison of PFS of both groups.

A comparison between *SDHx* PV positive and negative patients is described in Table 4. As anticipated, *SDHx* PV-negative patients were older than their *SDHx* PV-positive counterparts (*SDHx* PV-positive vs negative: 51±11 years vs 67±13 years, p-value = 0.022). There was no significant difference in the rates of hypertension according to *SDHx* PV status (positive vs negative, 60% vs 83%, p-value 0.492). Values of PFNMN did not differ pre-treatment but *SDHx* PV-positive versus negative patients had lower PFNMN post-treatment (*SDHx* PV-positive: median 936, IQR 7340 vs *SDHx* negative: median 28536, IQR 19066, p-value = 0.032).

HRQoL analysis

The HRQoL analysis, as assessed by the EORTC linear transformation of scores obtained from the QLQ-GINET21 questionnaire, revealed an overall trend of decreasing scores across PRRT cycles (Figure 5A), indicative of an improvement. The baseline score was 60.8 prior to the 1st cycle of PRRT (n=13), with a marginal decrease to 59.6 after the 1st cycle (n=12), and 52.3 after the 2nd cycle (n=7). For the patients who underwent four cycles of PRRT, the QLQ-GINET21 scores were 53.8 after the 3rd cycle (n=6) and 50.00 after the 4th cycle (n=2).

Endocrine symptoms (ES) initially worsened following the 1st cycle of PRRT, as indicated by an increase in the linear score from 51.3 at baseline to 63.9 (QLQ-GINET21 items 31-33). However, there was a gradual and sustained improvement in ES severity in subsequent cycles; the reported ES scores decreased to 42.9 and 44.4 following the 2nd and 4th cycles of PRRT, respectively (Figure 5B). Similarly, treatment-related symptoms (TR) improved across cycles

 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

(QLQ-GINET21 items 39-40); the TR score decreased from 40.48 after the 1st cycle to 37.5 after the 2nd cycle, and 33.3 after the 4th cycle (Figure 5C).

DISCUSSION:

In our total patient cohort, the number of male and female participants was comparable (male n=11, female n=9), with more than one-third (n=16, 80%) diagnosed with mPPGL. These patients underwent a median of 4 cycles of PRRT with a median cumulative dose of 29.7 GBq. The overall median follow-up period from the commencement of PRRT therapy was 29 months (5-134 months). Notably, our findings align with the outcomes of various recent retrospective studies (for a summary, see supplementary table 4).

Within our cohort of patients with mPPGL, the disease control rate (DCR) was 65%, which is lower than that reported in most other studies (where DCR generally exceeded 80%). Additionally, the median PFS in our cohort was 24 months, falling within the lower range of other studies reviewed in Supplemental Table 4 except for one prospective phase II clinical trial, in which an interim analysis of the safety and efficacy of ^{177}Lu-DOTATATE in metastatic or inoperable PPGL patients showed a DCR of >80% in the overall cohort, but 72% in patients with *SDHx* PV; the mean PFS was 19.1 months (overall), 22,7 months (sporadic PPGL) and 15.4 months (*SDHx* PV) [21]. In a recent review, Pacak and colleagues have summarised meta-analyses and seminal studies carried out in these patients using PRRT [7]. The divergence in DCR compared to the existing literature may potentially be attributed to a combination of factors, including one patient who experienced disease progression after PRRT due to receiving only two cycles at a reduced dose (half dose) of ^{177}Lu-DOTATATE, which was necessitated by pre-existing thrombocytopenia. Moreover, in our cohort 13 patients (65%) had 2 or more previous lines of treatment indicating higher disease burden at baseline compared to studies done previously, as shown in Supplemental Table 4. Remarkably, 75% of patients with phaeochromocytoma (PCC) showed stable disease following PRRT. Although some of the patients with progressive disease at the start of the PRRT had received other treatments (e.g. chemotherapy) before PRRT therapy, it is unlikely to have had any additive effects on the

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outcome as the disease progressed after receiving other treatments before PRRT was offered. It is also essential to acknowledge that our study cohort was limited in terms of the patient sample size. Of note, after a detailed analysis of the radiological behaviour of the disease, we observed that our patients commonly exhibited a non-significant *increase* in the size of bone and liver lesions post-PRRT. Whether this is of pathological concern or represents 'pseudo-progression' (i.e. the radiological appearance of progression when lesions undergo necrosis/apoptosis) is unclear. On the contrary, the size of peritoneal lesions *regressed* non-significantly following PRRT treatment. Although we did not routinely use molecular imaging for the assessment of treatment response post-PRRT, there is ongoing debate on whether molecular imaging would be better compared to cross-sectional imaging to assess treatment response post-PRRT. Recently updated Nuclear Medicine guidelines recommend SSTR-PET scan to be done 9-12 months post-PRRT to serve as a new baseline molecular imaging scan for future comparisons [22]. Additionally, the future use of quantitative measures such as serial or whole-body uptake parameters and changes in volumetric data in molecular/functional imaging will likely serve as important biomarkers for restaging, but further evaluation and prospective studies are warranted [23].

Analysis of the toxicity profile of PRRT in our cohort showed that PRRT therapy was well tolerated by patients. None of the patients developed grade 3 or 4 cytotoxicity. Compared to other studies on mPPGL, this was in the lower half of the range (grade 3 or 4 cytotoxicity: 0-30%) (Supplemental Table 4). None of the patients developed grade 3 or 4 nephrotoxicity, which is comparable to other studies. (Supplementary Table 4). It is noted that studies on PRRT therapy for GEP-NEN show that it is associated with 5-10% risk of CTCAE Grade 3/4 bone marrow toxicity [24]. Only 3 patients experienced an increase in blood pressure post-PRRT, which is also comparable with the previous studies[25]. In 6 patients, PFNMN levels increased after PRRT, and of these 6 patients, 2 patients had progressive disease. A recent study showed

a transient increase in plasma catecholamine (noradrenaline, adrenaline, dopamine and normetanephrine) especially 24 and 48 hours post-PRRT therapy, but the levels returned to baseline by day 30 [26]. None of our patients with secretory mPPGL developed tumour lysis syndrome or a catecholaminergic crisis after PRRT. It is worth noting that all patients with secretory mPPGL received adequate α-adrenoceptor blockade before PRRT therapy, which could have masked any catecholaminergic related changes.

We were unable to highlight a difference in the rate of disease control between *SDHx* positive and negative patients (60% vs 66%), while the median PFS appeared to be somewhat higher in the *SDHx*-negative group (*SDHx* positive versus negative, median PFS 21 months vs 45 months), although this was not statistically significant. Our results indicate that PRRT treatment efficacy with regards to disease control is comparable between pathogenic variant carriers and non-carriers, although our numbers are small. One study evaluated the effect of ^{90}Y-DOTATATE therapy in mPPGL related to *SDHx* pathogenic variants[25] . However, to our knowledge, there is no current comparative study done to compare the effect of ^{177}Lu DOTATATE PRRT therapy in positive and negative groups for genetic PVs.

In addition to the observed disease effects, PRRT in our mPPGL cohort demonstrated an overall improvement in reported symptoms throughout therapy, as evidenced by the increase in QLQ-GINET21 scores. Previous studies have established that PRRT improves HRQoL in patients with GEP-NENs [27–29]. However, the literature on HRQoL in this specific patient population remains limited. Yadav *et al.* reported an improvement in HRQoL scores in paraganglioma patients undergoing PRRT in combination with capecitabine therapy [30]. Notably, an initial exacerbation of endocrine symptoms was observed, followed by an improvement from baseline with subsequent treatment cycles. The reason for the initial exacerbation of endocrine symptoms with treatment is not completely understood.

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Furthermore, the reported treatment-related symptoms underscore the tolerability and safety profile of PRRT in this cohort, a finding consistent with previous studies involving other NET subtypes [31].

Limitations:

The current study has notable limitations that need to be taken into account when interpreting its findings. The primary limitation is the small sample size which, coupled with the retrospective study design, has restricted the statistical power and generalisability of the results. Furthermore, missing values of PFMN at various follow-up time points prohibited us from a pairwise comparison. Hence, the role of PRRT in the catecholamine-secreting capacity of mPPGL could not be fully assessed. From the cohort of patients who progressed through the PRRT treatment, one patient received 2 cycles of half the standard dose of ^{177}Lu-DOTATATE and they had extensive disease burden at the start of the therapy. Finally, given the retrospective nature of this study, we could not reliably confirm administration of specific bone-agents to this cohort of patients for those eligible to receive this type of treatment. Furthermore, there were significant limitations in the HRQoL analysis, including a limited sample size and a low questionnaire completion rate, particularly in later PRRT cycles. As a result, meaningful statistical analysis was not feasible, and a narrative analysis was performed instead. The QLQ-GINET21 is commonly used to assess HRQoL in NET patients; however, it is important to note that it has been validated in the GEP-NEN cohort, and there is currently no specific validated questionnaire for patients with mPPGL. While the QLQ-C30 remains a reasonable alternative, it was not utilised at the time of the study in accordance with local guidelines. Additionally, although not formally validated for this cohort, the EORTC QLQ-H&N might

have been a suitable alternative for assessing HRQoL in patients with head and neck paragangliomas.

Conclusions:

PRRT, employing ^{177}Lu-DOTATATE PRRT, has been shown to be a safe and effective method for managing metastatic or inoperable PPGL, with low toxicity and an encouraging PFS. Considering radiological changes evidenced during disease, PRRT appears to sufficiently control peritoneal metastatic spread but the effect on the progression of disease in the bones remains unclear. It also appears to improve HRQoL in patients with mPPGL. Our experience is concordant with the currently available evidence on the effectiveness of PRRT in mPPGL, suggesting that it should be seriously considered as first-line treatment for patients with slowly to moderately growing m-PPGL with moderate to high tumour burden, considering the fact that it is extremely difficult to conduct and complete prospective clinical trials in this rare tumour that rarely metastasise and require systemic therapy[7,32–35]. A phase II prospective trial of ^{177}Lu-DOTATATE (*Lutathera*®) PRRT for unlicenced indications is currently recruiting patients which include patients with mPPGL with an estimated completion by the end of 2027 (NCT06121271). Additionally, newer targeted therapeutic agents, either alone or in combination with PRRT, are being explored to treat these rare and complex tumours.

Authors contributions:

Kalyan Mansukhbhai Shekhda: writing – original draft, review and editing, statistical analysis. Eleni Armeni: writing – review and editing, statistical analysis, supervision. Yiwang Xu: writing – review and editing. Manfredi D'afflitto: writing – review and editing, statistical analysis.

 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

Shaunak Navalkissoor: writing – review and editing. Christos Toumpanakis: writing – review and editing. Dalvinder Mandair: writing – review and editing, Aimee Hayes: writing – review and editing. Dominic Yu: writing – review and editing. Ann-Marie Quigley: writing – review and editing. Gopinath Gnanasegaran: writing – review and editing. Ashley Grossman: writing – review and editing. Martyn Caplin: writing – review and editing. Bernard Khoo: Conceptualization, supervision, writing – review and editing.

Funding statement:

No funding was obtained for this study.

Conflict of interest:

The authors have no conflict of interest to declare.

Ethical approval statement: As this study was retrospective audit of practice, ethical approval was not required under the UK Policy Framework for Health and Social Care Practice. Audit registration number: RFH_23/24678.

References:

[1] Patel D, Phay JE, Yen TWF, Dickson P V, Wang TS, Garcia R, et al. Update on Pheochromocytoma and Paraganglioma from the SSO Endocrine/Head and Neck Disease-Site Work Group. Part 1 of 2: Advances in Pathogenesis and Diagnosis of Pheochromocytoma and Paraganglioma. Ann Surg Oncol 2020;27:1329–37. https://doi.org/10.1245/s10434-020-08220-3.

[2] Jaiswal SK, Sarathi V, Memon SS, Goroshi M, Jadhav S, Prakash G, et al. SYMPATHETIC PARAGANGLIOMA: A SINGLE-CENTER EXPERIENCE FROM WESTERN INDIA. Endocr Pract 2019;25:211–9. https://doi.org/10.4158/EP-2018-0480.

[3] Nölting S, Bechmann N, Taieb D, Beuschlein F, Fassnacht M, Kroiss M, et al. Personalized Management of Pheochromocytoma and Paraganglioma. Endocr Rev 2022;43:199–239. https://doi.org/10.1210/endrev/bnab019.

[4] Roman-Gonzalez A, Zhou S, Ayala-Ramirez M, Shen C, Waguespack SG, Habra MA, et al. Impact of Surgical Resection of the Primary Tumor on Overall Survival in Patients With

Metastatic Pheochromocytoma or Sympathetic Paraganglioma. Ann Surg 2018;268:172–8. https://doi.org/10.1097/SLA.0000000000002195.

[5] Fischer A, Kloos S, Remde H, Dischinger U, Pamporaki C, Timmers HJLM, et al. Responses to systemic therapy in metastatic pheochromocytoma/paraganglioma: a retrospective multicenter cohort study. Eur J Endocrinol 2023;189:546–65. https://doi.org/10.1093/ejendo/lvad146.

[6] Nölting S, Grossman A, Pacak K. Metastatic Phaeochromocytoma: Spinning Towards More Promising Treatment Options. Exp Clin Endocrinol Diabetes 2019;127:117–28. https://doi.org/10.1055/a-0715-1888.

[7] Pacak K, Taieb D, Lin FI, Jha A. Approach to the Patient: Concept and Application of Targeted Radiotherapy in the Paraganglioma Patient. J Clin Endocrinol Metab 2024;109:2366–88. https://doi.org/10.1210/clinem/dgae252.

[8] Carrasquillo JA, Chen CC, Jha A, Pacak K, Pryma DA, Lin FI. Systemic Radiopharmaceutical Therapy of Pheochromocytoma and Paraganglioma. Journal of Nuclear Medicine 2021;62:1192–9. https://doi.org/10.2967/jnumed.120.259697.

[9] van Hulsteijn LT, Niemeijer ND, Dekkers OM, Corssmit EPM. ^{131}I- <scp>MIBG</scp> therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. Clin Endocrinol (Oxf) 2014;80:487–501. https://doi.org/10.1111/cen.12341.

[10] Sze WCC, Grossman AB, Goddard I, Amendra D, Shieh SCC, Plowman PN, et al. Sequelae and survivorship in patients treated with 131I-MIBG therapy. Br J Cancer 2013;109:565–72. https://doi.org/10.1038/bjc.2013.365.

[11] Urso L, Nieri A, Uccelli L, Castello A, Artioli P, Cittanti C, et al. Lutathera® Orphans: State of the Art and Future Application of Radioligand Therapy with 177Lu-DOTATATE. Pharmaceutics 2023;15:1110. https://doi.org/10.3390/pharmaceutics15041110.

[12] Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017;376:125–35. https://doi.org/10.1056/NEJMoa1607427.

[13] Elston MS, Meyer-Rochow GY, Conaglen HM, Clarkson A, Clifton-Bligh RJ, Conaglen J V, et al. Increased SSTR2A and SSTR3 expression in succinate dehydrogenase-deficient pheochromocytomas and paragangliomas. Hum Pathol 2015;46:390–6. https://doi.org/10.1016/j.humpath.2014.11.012.

[14] Satapathy S, Mittal BR, Bhansali A. “Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: A systematic review and meta-analysis”. Clin Endocrinol (Oxf) 2019;91:718–27. https://doi.org/10.1111/cen.14106.

[15] Morse B, Jeong D, Ihnat G, Silva AC. Pearls and pitfalls of response evaluation criteria in solid tumors (RECIST) v1.1 non-target lesion assessment. Abdom Radiol (NY) 2019;44:766–74. https://doi.org/10.1007/s00261-018-1752-4.

[16] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24. https://doi.org/10.1038/gim.2015.30.

 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

[17] Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1—Update and clarification: From the RECIST committee. Eur J Cancer 2016;62:132–7. https://doi.org/10.1016/j.ejca.2016.03.081.

[18] Nishino M. Tumor Response Assessment for Precision Cancer Therapy: Response Evaluation Criteria in Solid Tumors and Beyond. Am Soc Clin Oncol Educ Book 2018;38:1019–29. https://doi.org/10.1200/EDBK_201441.

[19] Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017.

[20] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI Journal of the National Cancer Institute 1993;85:365–76. https://doi.org/10.1093/jnci/85.5.365.

[21] Lin F, Carrasquillo J, del Rivero J, Shamis I, Zou J, Turkbey B, et al. Safety and efficacy of Lu-177-DOTATATE in metastatic or inoperable phaeochromocytoma/paraganglioma- an interim analysis. Journal of Nuclear Medicine 2023;64:P1296.

[22] Hope TA, Allen-Auerbach M, Bodei L, Calais J, Dahlbom M, Dunnwald LK, et al. SNMMI Procedure Standard/EANM Practice Guideline for SSTR PET: Imaging Neuroendocrine Tumors. Journal of Nuclear Medicine 2023;64:204–10. https://doi.org/10.2967/jnumed.122.264860.

[23] Kong G, Noe G, Chiang C, Herrmann K, Hope TA, Michael M. Assessment of response to PRRT including anatomical and molecular imaging as well as novel biomarkers. J Neuroendocrinol 2025;37:e13461. https://doi.org/10.1111/jne.13461.

[24] Alsadik S, Gnanasegaran G, Chen L, Quigley A-M, Mandair D, Toumpanakis C, et al. Safety and Efficacy of 177Lu-DOTATATE in Neuroendocrine Tumor Patients With Extensive Bone Disease. Clin Nucl Med 2023;48:667–72. https://doi.org/10.1097/RLU.0000000000004671.

[25] Kolasinska-Ćwikła A, Pęczkowska M, Ćwikła J, Michałowska I, Pałucki J, Bodei L, et al. A Clinical Efficacy of PRRT in Patients with Advanced, Nonresectable, Paraganglioma-Pheochromocytoma, Related to SDHx Gene Mutation. J Clin Med 2019;8:952. https://doi.org/10.3390/jcm8070952.

[26] Gubbi S, Al-Jundi M, Auh S, Jha A, Zou J, Shamis I, et al. Early short-term effects on catecholamine levels and pituitary function in patients with pheochromocytoma or paraganglioma treated with [177Lu]Lu-DOTA-TATE therapy. Front Endocrinol (Lausanne) 2023;14. https://doi.org/10.3389/fendo.2023.1275813.

[27] Marinova M, Mücke M, Mahlberg L, Essler M, Cuhls H, Radbruch L, et al. Improving quality of life in patients with pancreatic neuroendocrine tumor following peptide receptor radionuclide therapy assessed by EORTC QLQ-C30. Eur J Nucl Med Mol Imaging 2018;45:38–46. https://doi.org/10.1007/s00259-017-3816-z.

[28] Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of Life in 265 Patients with Gastroenteropancreatic or Bronchial Neuroendocrine Tumors Treated with [^{177} Lu-DOTA ^{0} ,Tyr ^{3}]Octreotate. Journal of Nuclear Medicine 2011;52:1361–8. https://doi.org/10.2967/jnumed.111.087932.

[29] Harris PE, Zhernosekov K. The evolution of PRRT for the treatment of neuroendocrine tumors; What comes next? Front Endocrinol (Lausanne) 2022;13. https://doi.org/10.3389/fendo.2022.941832.

[30] Yadav MP, Ballal S, Bal C. Concomitant 177Lu-DOTATATE and capecitabine therapy in malignant paragangliomas. EJNMMI Res 2019;9:13. https://doi.org/10.1186/s13550-019-0484-y.

[31] Edfeldt K, Hellman P, Granberg D, Lagergren P, Thiis-Evensen E, Sundin A, et al. Improved health-related quality of life during peptide receptor radionuclide therapy in patients with neuroendocrine tumours. J Neuroendocrinol 2023;35. https://doi.org/10.1111/jne.13342.

[32] Tang CYL, Chua WM, Huang HL, Lam WW, Loh LM, Tai D, et al. Safety and efficacy of peptide receptor radionuclide therapy in patients with advanced pheochromocytoma and paraganglioma: A single-institution experience and review of the literature. J Neuroendocrinol 2023;35. https://doi.org/10.1111/jne.13349.

[33] Garcia-Carbonero R, Matute Teresa F, Mercader-Cidoncha E, Mitjavila-Casanovas M, Robledo M, Tena I, et al. Multidisciplinary practice guidelines for the diagnosis, genetic counseling and treatment of pheochromocytomas and paragangliomas. Clinical and Translational Oncology 2021;23:1995–2019. https://doi.org/10.1007/s12094-021-02622-9.

[34] Casey RT, Hendriks E, Deal C, Waguespack SG, Wiegering V, Redlich A, et al. International consensus statement on the diagnosis and management of phaeochromocytoma and paraganglioma in children and adolescents. Nat Rev Endocrinol 2024;20:729–48. https://doi.org/10.1038/s41574-024-01024-5.

[35] Nölting S, Ullrich M, Pietzsch J, Ziegler CG, Eisenhofer G, Grossman A, et al. Current Management of Pheochromocytoma/Paraganglioma: A Guide for the Practicing Clinician in the Era of Precision Medicine. Cancers (Basel) 2019;11:1505. https://doi.org/10.3390/cancers11101505.

Figure Legends

Figure 1: Flow chart of inclusion process of study cohort.

Figure 2: Comparison of progression free survival (PFS) for phaeochromocytoma (PCC) and paraganglioma (PGL) patients.

Figure 3: Comparison of progression free survival (PFS) for *SDHx* positive and negative patient groups

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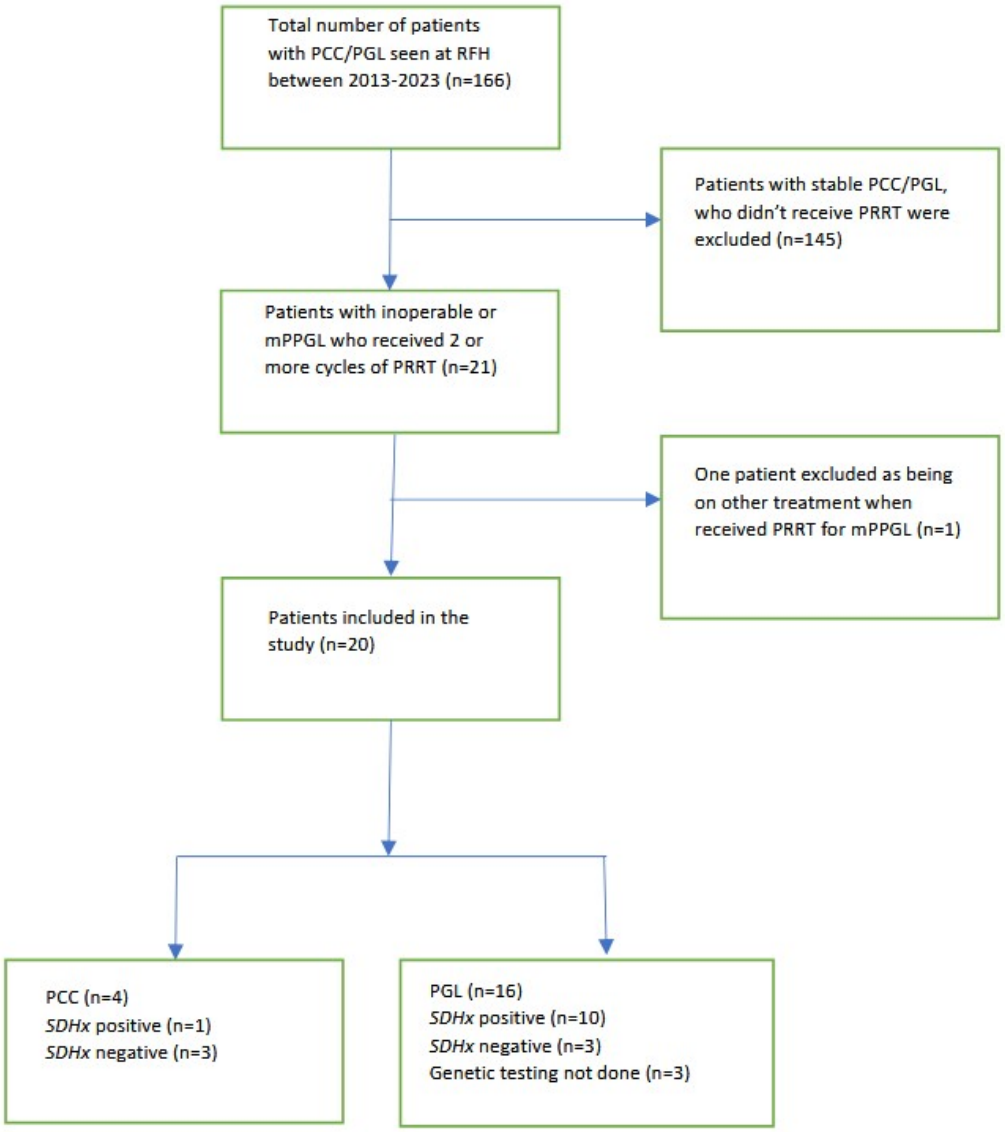
Figure 4. The mean difference in the sum of the longest diameter of the target lesions at baseline and follow up.

Figure 5 HRQOL scores based on QLQ-GINET21 linear scale before and following each cycle of PRRT (A). Endocrine specific symptoms (ED) (B) and treatment-related symptoms (TR)(C) linear scales throughout PRRT therapy.



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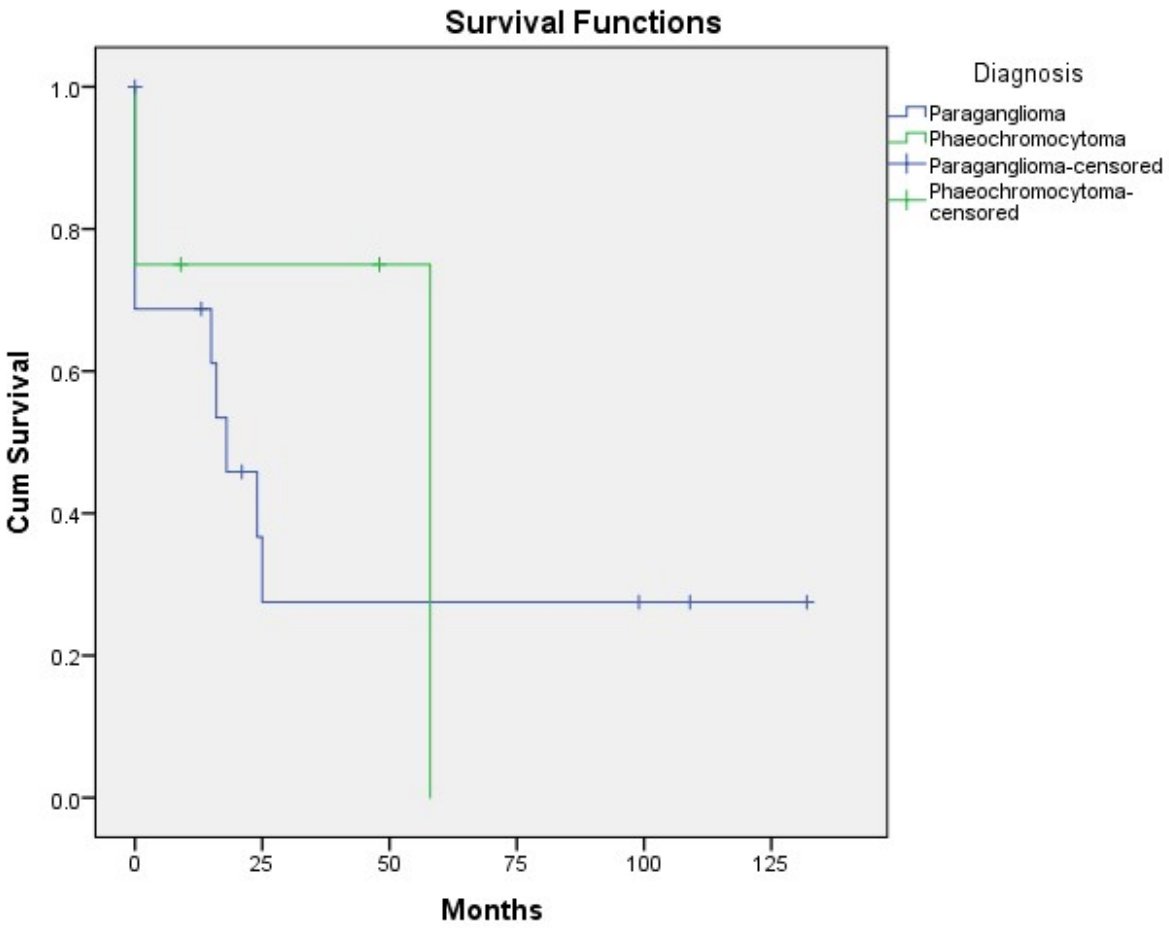

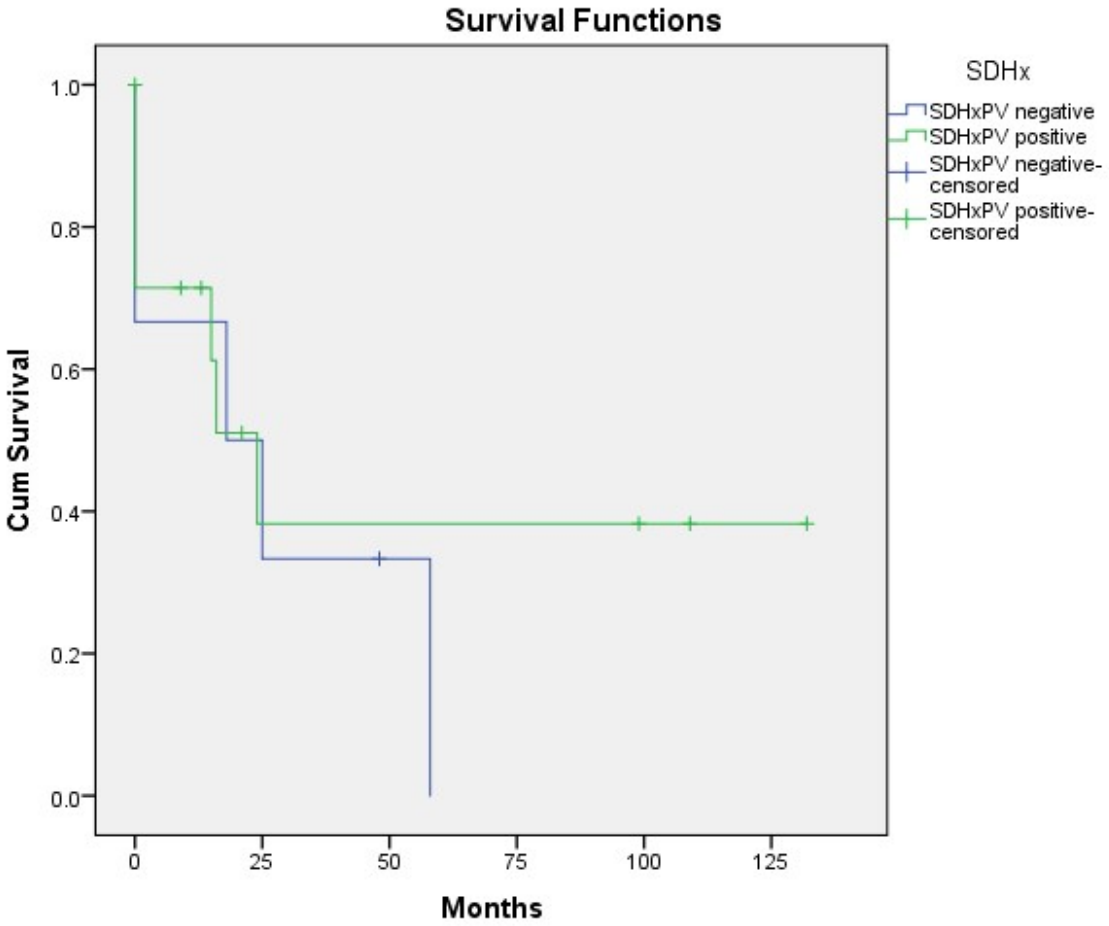

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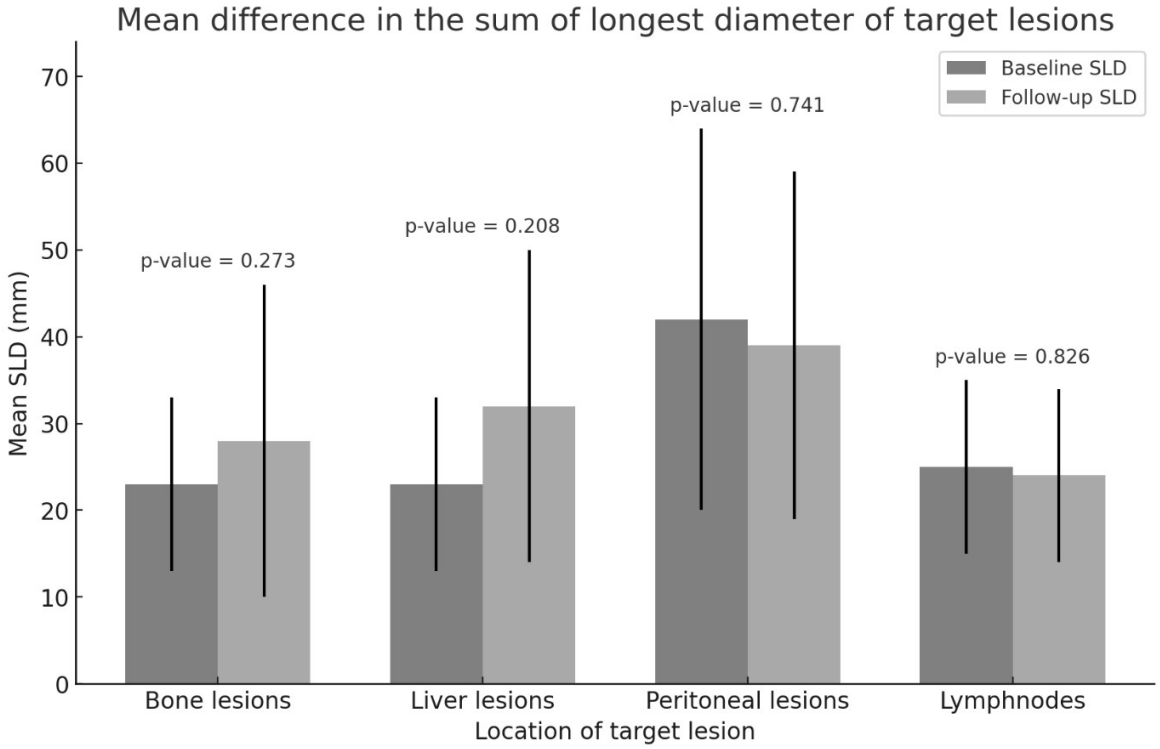

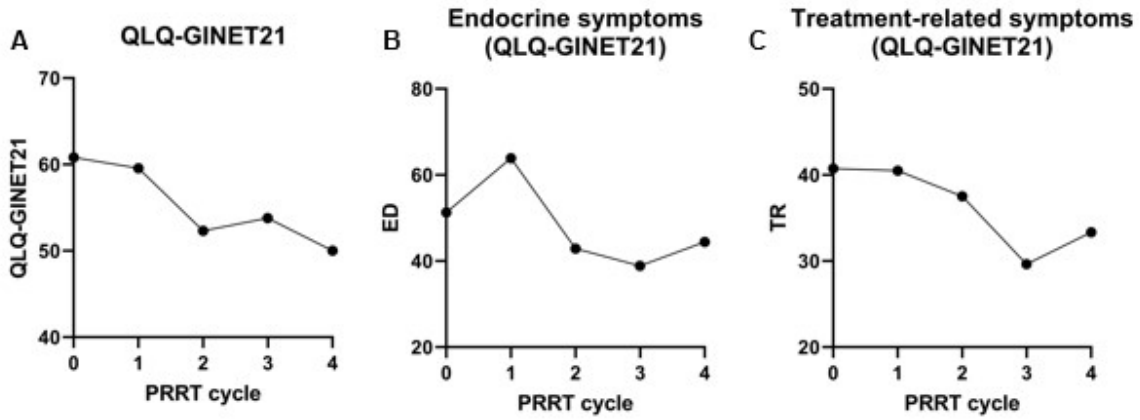

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Table 1: Demographic summary of the study cohort (n=19)

Gender n (%)	Absolute number (Frequency, %) or mean±SD
Male	11 (55%)
Female	9 (45%)
Age (years)	58 ± 14
Primary tumour n (%)	
PCC	4 (20%)
PGL	16 (80%)
Secretory n (%)	
Yes	10 (50%)
No	5 (25%)
Unknown	5 (25%)
Carrier of *SDHx* germline pathogenic variations n (%)	
Yes	11 (55%)
No	6 (32%)
Unknown	3 (16%)
Previous treatment history for mPPGL	
Surgery of primary tumour	17 (85%)
MIBG therapy	3 (15%)
SST analogues	6 (30%)
Chemotherapy (CVD or CapTem)	4 (20%)
Molecular targeted therapy (sunitinib or sorafenib)	2 (10%)

Radiotherapy	4 (20%)
98-Yttrium Octreate therapy	1 (10%)
Previous number of treatments received	
0	2 (10%)
1	5 (25%)
2	9 (45%)
3	2 (10%)
4	2 (10%)
PRRT Lu^{177} characteristics	
Median number of cycles	4 (2-4)
Cumulative dose of treatment (GBq)	24.55 ± 7.77
Median follow up (months)	29 months (5-134, IQR: 58)

n, number of patients; M, male; F, female; SD, Standard Deviation; PCC, Phaeochromocytomas; PGL, Paragangliomas; PRRT, Peptide Receptor Radionuclide Treatement; GBq, gigabecquerel; *SDHx*, Succinate dehydrogenase subunits A-D; IQR, Interquarantile range.

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Table 2: Radiological features and RECIST assessment of the study cohort.

Radiological features and RECIST assessment of the study cohort	
Indication for PRRT n (%)	
Progressive disease	17 (85%)
Inoperable disease	3 (15%)
Total number of patients	20 (100%)
Site of metastasis n	
Lungs	3
Liver	5
Adrenals	3
Lymphnodes	7
Bones	11
Peritoneum	6
SLD (in mm) (mean ± S.D)	
Baseline	101 ± 59 mm
Follow up	108 ± 66 mm (P: 0.73)
SLD change percentage post PRRT (mean ± SD)	6 ± 20
Non target status post PRRT n(%)	

Progressed	4 (20%)
Stable	15 (75%)
Disappeared	1 (15%)
New lesion n (%)	7 (35%)
Post PRRT RECIST assessment n(%)	
Stable disease	12 (60%)
Progressive disease	7 (35%)
Partial response	1 (5%)

n, number of patients; RECIST, Radiological Evaluation Criteria in Solid Tumour; PRRT, Peptide Receptor Radionuclide Therapy; SLD, Single Lesion Diameter; SD, Standard Deviation; mm, millimetre

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Table 3: Clinical features (side effects) and changes in antihypertensives pre and post PRRT.

Clinical and biochemical features of the study cohort	
Use of anti-hypertensives n (%)	
Pre PRRT	
Patients on antihypertensives:	12 (60%)
Patients not on antihypertensives	8 (40%)
Post PRRT	
Patients on antihypertensives	12 (60%)
Patients not on antihypertensives	8 (40%)
Changes in anti-hypertensives post PRRT n (%)	
Increased	3 (15%)
No changes	17 (85%)
Number of patients with PFNMN levels n (%)	
Pre-PRRT	
Elevated PFNMN	8 (40%)
Normal PFNMN	6 (30%)
PFNMN not available	6 (30%)

Post PRRT	
Elevated PFNMN	6 (30%)
Normal PFNMN	5 (25%)
PFNMN not available	9 (45%)
Minor side effects	
Fatigue	5(25%)
Bony pain	4 (20%)
Nausea	2 (10%)
Hiccups	1 (5%)
Grade 2 Anaemia	2 (10%)
Grade 1 Thrombocytopenia	2 (10%)
Major side effects	
Nephrotoxicity	0(0%)
Grade 3/4 cytopenia n (%)	0(0%)

n, number of patients; PRRT, Peptide Receptor Radionuclide treatment; PFNMN, Plasma Free Normetanephrines; SD, Standard Deviation

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Table 4 : Comparison between *SDHx* PV carriers vs non-*SDHx* group.

Parameter		P value (95% CI)
	Mean age (years)	
SDHx PV positive group	49 ± 12	0.012
SDHx PV negative group	67± 13	
	Tumour type (n)	
SDHx PV positive group	PGL: 10	0.476
	PCC: 1	
SDHx PV negative group	PGL: 3	
	PCC: 3	
	Hypertension n (%)	
SDHx PV positive group	6 (60%)	0.492
SDHx PV negative group	5 (83%)	
	Pre-therapy PFNMN [median (min-max, IQR)]	
SDHx PV positive group	1124 (408-40000; 39309)	0.298
SDHx PV negative group	23169.5 (18125-31668; 8882)	
	Post-therapy PFNMN [median (min-max, IQR)]	
SDHx PV positive group	747(110-9404; 5740)	0.662

SDHx PV negative group	28536 (6159,35500; 19065.5)	
No of PRRT cycles [median (min-max, IQR)]		
SDHx PV positive group	4 (2-4; 2)	0.275
SDHx PV negative group	4(2-4 ; 0)	
Mean cumulative dose of Lu (GBq) (mean ± SD)		
SDHx PV positive group	22.731 ± 8.923	0.247
SDHx PV negative group	27.673 ± 6.032	
Stable disease and partial response n (%)* at the end		
SDHx PV positive group	7 (64%)	1
SDHx PV negative group	4 (67%)	
Progression free survival months (mean ± SD)		
SDHx PV positive group	30 ± 38	0.8210
SDHx PV negative group	26 ± 25	

Statistical significance was defined as p-value < 0.05

SDHx, Succinate dehydrogenase subunits A-B; n, number of patients; PGL, paraganglioma; PCC, Phaeochromocytoma; PFNMN, plasma free non-metanephrines; SD, standard deviation; PRRT, peptide receptor radionuclide therapy; GBq, Gigabecquerel; IQR, Interquarantile range

Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

Supplementary Files:

Supplementary Figure 1: EORTC NET-specific questionnaire QLQ-GINET21*

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

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 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

Supplemental Table 1: Baseline characteristics of the study cohort

Case no.	Sex	Age at the start of therapy	Primary tumour	Previous treatment history	Indication for PRRT	Site of metastasis	Secretory status	Number of PRRT cycles	Cumulative dose of PRRT (GBq)	Follow up (in months)	Germline PV
1	Male	72	PCC	Surgery, MIBG	PD	Lung,Liver, Lymphnodes	N/D	4	29.831	59	Negative
2	Male	61	PCC	Nil	Inoperable disease	Adrenal, Bone	S	2	14.890	5	SDH-B
3	Female	69	PGL	Surgery	PD	Liver, Bone	S	2	15.805	75	SDH-B
4	Male	73	PGL	Surgery, CVD, sorafenib, SSTAs	PD	Bone	S	4	30.583	28	Negative
5	Female	44	PGL	Surgery, radiotherapy	PD	Bone	N/D	4	29.728	134	SDH-B
6	Female	84	PGL	Nil	Inoperable disease	Lymph nodes, bone	S	4	29.930	29	Negative
7	Male	60	PGL	Surgery, radiotherapy	PD	Peritoneum, Bone, Liver	NS	4	22.464	21	ND
8	Female	61	PGL	Surgery, SSTA	PD	Liver, Peritoneal	S	4	29.687	132	ND
9	Female	35	PGL	Surgery	PD	Lung, Bone	NS	4	29.775	109	SDH-B, SDH-D
10	Female	63	PGL	Surgery, MIBG therapy	PD	Liver, Bone	S	2	14.987	13	SDH-B
11	Male	47	PGL	Surgery, 98-Yttrium Octreate therapy	PD	Lymphnode, Peritoneum, Bone	S	4	29.841	15	SDH-B
12	Male	49	PGL	Surgery, SSTA	PD	Bone	NS	4	30.670	82	SDH-C

13	**Male**	44	**PGL**	**Surgery, Radiotherapy**	**PD**	**Skeletal lesions**	**N/D**	4	31.026	31	**SDH-B**
14	**Female**	61	**PGL**	**Surgery, MIBG therapy, Sunitinib, CapTem**	**PD**	**Lymphnode, Peritoneum**	**N/D**	2	15.516	29	**SDH-B**
15	**Male**	49	**PCC**	**Surgery**	**PD**	**Lymphnodes, Peritoneum**	**S**	4	30.994	**72**	**Negative**
16	**Female**	72	**PGL**	**Surgery, SSTAs, radiotherapy**	**PD**	**Bone**	**S**	4	28.548	10	**ND**
17	**Male**	55	**PGL**	**Surgery**	**PD**	**Adrenal, Peritoneal**	**N/D**	2	15.419	5	**Negative**
18	**Female**	77	**PCC**	**Surgery**	**PD**	**Lung, Lymphnode**	**S**	4	29.278	**48**	**Negative**
19	**Male**	49	**PGL**	**Surgery, CVD, SSTAs**	**PD**	**Adrenal, Lung**	**NS**	2	7.400	15	**SDH-B**
20	**Male**	30	**PGL**	**CVD chemotherapy, SSTAs**	**Inoperable disease**	**Pelvic mass**	**NS**	4	30,404	29	**SDH-B**

 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

Supplemental Table 2: Radiological features and RECIST assessment of the study cohort:

Case number	Indication for PRRT	Site of metastases	SLD change percentage post PRRT Mean±SD (%) (6 ± 20)	Non-target lesion status post PRRT n (%) Progressed n:4(21%) Stable n:14 (74%) Disappeared n:1 (5%)	New lesion? n:7 (37%)	Post PRRT RECIST assessment [Progressive disease n:7 (37%) Stable disease n:11 (58%) Partial response n:1 (5%)]
1	**Progressive disease**	**Lung,Liver, Lymph nodes**	52%	Progressed	Yes	Progressive disease
2	**Inoperable disease**	**Adrenal, Bone**	17%	Stable	No	Stable disease
3	**Progressive disease**	**Liver, Bone**	-2%	Stable	No	Stable disease
4	**Progressive disease**	**Bone**	-17%	Stable	No	Stable disease
5	**Progressive**	**Bone**	-12%	Stable	No	Stable disease
6	**Inoperable disease**	**Lymph nodes, bone**	36%	Stable	No	Stable disease
7	**Inoperable disease**	**Peritoneum, Bone, Liver**	20%	Stable	No	Stable disease
8	**Progressive disease**	**Liver, Peritoneal**	-1%	Stable	No	Stable disease
9	**Progressive disease**	**Lung, Bone**	-31%	Stable	No	Partial response
10	**Progressive disease**	**Liver, Bone**	10%	Stable	No	Stable disease
11	**Progressive disease**	**Lymphnode, Peritoneum, Bone**	6%	Stable	Yes	Progressive disease
12	**Progressive disease**	**Bone, Lymph nodes**	136%	Stable	Yes	Progressive disease
13	**Progressive disease**	**Skeletal lesions**	0%	Stable	No	Stable disease
14	**Progressive disease**	**Lymph node, Peritoneum**	-3%	Disappeared	Yes	Progressive disease
15	**Progressive disease**	**Lymph nodes, Peritoneum**	-7%	Stable	No	Stable disease
16	**Progressive disease**	**Bone**	0%	Progressed	Yes	Progressive disease
17	**Progressive disease**	**Adrenal, Peritoneal**	52%	Progressed	Yes	Progressive disease
18	**Progressive disease**	**Lung, Lymph node**	-9%	Stable	No	Stable disease

19	**Progressive disease**	**Adrenal, Lung**	14%	Progressed	Yes	Progressive disease
20	**Progressive disease**	**Pelvic mass**	-16%	Stable	No	Stable disease

Supplemental Table 3: Clinical features (side effects) and changes in antihypertensives pre and post PRRT:

Case number	AntiHTN (before therapy)	AntiHTN (after therapy)	Changes in antihypertensive therapy	Plasma normetanephrines		Side effects (after therapy)		
				Baseline	Post PRRT	Nephro toxicity	Cyto penia	Others
1	Candesartan 12mg	Candesartan 16mg	Increased	Not available	Not available	Nil	Nil	Fatigue, nausea
2	Propranolol 40mg Candesartan 8mg Phenoxybenzamine 20mg	Propranolol 40mg Candesartan 8mg Phenoxybenzamine 20mg	No change	Not available	Not available	Nil	Nil	Hiccups
3	Doxazocin 2mg	Doxazocin 2mg	No change	Elevated	Elevated	Nil	Nil	Fatigued, tremors, Shingles
4	Amlodipine 10mg	Amlodipine 10mg Doxazocin 16mg	Increased	Elevated	Elevated	Nil	Nil	-
5	Doxazocin 8mg Atenolol 100mg	Doxazocin 8mg Atenolol 100mg	No change	Not available	Normal	Nil	Nil	-
6	Amlodipine 5mg Atenolol 50mg Doxazocin 2mg	Amlodipine 5mg Atenolol 50mg Doxazocin 2mg	No change	Elevated	Elevated	Nil	Nil	-
7	No Antihypertensives	No Antihypertensives	No change	Normal	Normal	Nil	Nil	-
8	No Antihypertensives	No Antihypertensives	No change	Elevated	Not available	Nil	Nil	Pain
9	No Antihypertensives	No Antihypertensives	No change	Normal	Normal	Nil	Nil	-
10	Phenoxybenzamine 30mg Propranolol 20mg	Phenoxybenzamine 30mg	No change	Elevated	Not available	Nil	Nil	Fatigue, pain

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		Propranolol 20mg						
11	Doxazocin 1mg	Doxazocin 1mg	No change	Not available	Elevated	Nil	Nil	Fatigue
12	No Antihypertensives	No Antihypertensives	No change	Normal	Not available	Nil	Nil	-
13	No Antihypertensives	No Antihypertensives	No change	Not available	Normal	Nil	Nil	Nil
14	Phenoxybenzamine 40mg Propranolol 40mg Losartan 100mg Lercanidipine 10mg	Phenoxybenzamine 40mg Propranolol 40mg Losartan 100mg Lercanidipine 10mg	No change	Not available	Not available	Nil	Nil	Low platelets
15	Bisoprolol 2.5mg Doxazocin 4mg	Bisoprolol 2.5mg Doxazocin 4mg	No change	Elevated	Elevated	Nil	Nil	Fatigue, nausea
16	Bisoprolol Doxazocin Furosemide	Not available	Not available	Elevated	Not available	Nil	Nil	Neck pain
17	No Antihypertensives	No antihypertensives	No change	Not available	Not available	Nil	Nil	Bony pain, Constipation, sickness
18	Phenoxybenzamine 10mg Doxazocin 3mg	Phemoxybenzamine 40mg Doxazocin 4mg	Increased	Elevated	Elevated	Nil	Nil	Hair loss
19	No antihypertensives	No antihypertensives	No change	Normal	Not available	Nil	Nil	Nil
20	No antihypertensives	No antihypertensives	No change	Normal	Normal	Nil	Nil	Fatigue, Diarrhoea

Supplementary Table 4: Comparison between various studies of Peptide Receptor Radionuclide Therapy (PRRT) in Phaeochromocytomas and paragangliomas (PPGL)

	Year	Number of patients	Type of study	Bone metastases at baseline	*SDHx* PV status	Response rate	Survival (months)	Follow up duration (months)	Grade 3 / 4 Toxicity
Kolasinka-Cwikla et al [1]	2019	Total: 13 PCC: 0 PGL: 13	PS	70%	*SDHx* positive: 13	CR: 0% PR: 8% SD: 75% PD: 17% DCR: 92%	Median OS: 68 Median PFS: 35	48	Nephrotoxicity: 0% Bone marrow toxicity: 15%
Zandee WT et al [2]	2019	Total: 30 PCC: 3 PGL: 27	RS	N/A	*SDHx* positive: 16 *SDHx* negative: 7 NA: 7	CR: 0% PR: 23% SD: 67% PD: 10% DCR: 90%	Median OS: NR Median PFS: 30	52.5	Nephrotoxicity: NA Bone marrow toxicity: 20%
Kong G et al [3]	2017	Total: 20 PCC: 8 PGL: 11 Organ of Zuckerkandl: 1	RS	N/A	*SDHx* positive: 8 *SDHx* negative: 2 NA: 10	CR: 0% PR: 29% SD: 50% PD: 14% DCR: 795	Median OS: NR Median PFS: 39	28	Nephrotoxicity: 0% Bone marrow toxicity: 30%
Severi S et al[4]	2021	Total: 46 PCC: NA PGL: NA	Phase II clinical trial	41%	*SDHx* positive: 20 *SDHx* negative: 16 NA: 10	CR: 0 % PR: 9% SD: 72% PD: 19% DCR: 80%	Median OS: 143.5 Median PFS: NR	73	Nephrotoxicity: 0% Bone marrow toxicity: 0%

Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

Jaiswal SK et al[5]	2020	Total: 15 PCC: 5 PGL: 10	RS	40%	*SDHx* positive: 2 *SDHx* negative: 3 NA: 10	CR: 0% PR: 7% SD: 73% PD: 20% DCR: 80%	Median OS: NR Median PFS: NR	26	Nephrotoxicity: 0% Bone marrow toxicity: 0%
Vyakaranam A.R. et al [6]	2019	Total: 22 PCC: 9 PGL: 13	RS	77%	*SDHx* positive: 7 *SDHx* negative: 6 NA: 9	CR: 0% PR: 9% SD: 91% PD: 0% DCR: 100%	Median OS: 50 Median PFS: 22	32	Nephrotoxicity: 0% Bone marrow toxicity: 0%
Nastos et al[7]	2017	Total: 9 PCC: 1 PGL: 8	RS	78%	*SDHx* positive: 4 NA: 5	CR: 0% PR: NA SD: NA PD: NA DCR: NA	Median OS: 60 Median PFS: 39	39	Nephrotoxicity: 0% Bone marrow toxicity: 22%
Mitjavila M et al[8]	2022	Total: 31 PCC: NA PGL: NA	RS	65%	NA: 31	CR: 0% PR: 19% SD: 65% PD: 15% DCR: 85%	Median OS: NR Median PFS: 31	NA	Nephrotoxicity: NA Bone marrow toxicity: NA
Fischer A et al[9]	2023	Total: 22 PCC: NA PGL: NA	RS	NA	*SDHx* positive: 14 *SDHx* negative: 6 NA: 2	CR: 0% PR: N/A SD: N/A PD: N/A DCR: 67%	Median OS: NA Median PFS: 18	NA	Nephrotoxicity: NA Bone marrow toxicity: NA
Pinato et al[10]	2016	Total: 5 PCC: 0 PGL: 5	RS	100%	*SDHx* positive: 5 *SHDx* negative: 0	CR: 0% PR: 20% SD: 60% PD: 20% DCR: 80%	Median OS: NR Median PFS: 17	NA	Nephrotoxicity: NA Bone marrow toxicity: NA

Hamiditabar et al[11]	2017	Total: 5 PCC: 1 PGL: 4	PS	NA	NA: 5	CR: 0% PR: 0% SD: 80% PD: 20% DCR: 80%	Median OS: NA Median PFS: NA	NA	Nephrotoxicity: NA Bone marrow toxicity: NA
Demirci et al[12]	2018	Total: 8 PCC: NA PGL: NA	RS	NA	NA: 8	CR: 0% PR: 50% SD: 25% PD: 25% DCR: 75%	Median OS: 51.8 Median PFS: 31.4	NA	Nephrotoxicity: NA Bone marrow toxicity: NA
Yadav et al*[13]	2019	Total: 25 PCC: 0 PGL: 25	RS	52%	NA: 25	CR: 0% PR: 28% SD: 56% PD: 16% DCR: 84%	Median OS: NR Median PFS: 32	30	Nephrotoxicity: 0% Bone marrow toxicity: 0%
Roll et al[14]	2020	Total: 7 PCC: 0 PGL: 7	RS	14%	NA: 7	CR: 0% PR: 0% SD: 100% PD: 0% DCR: 100%	Median OS: NA Median PFS: NA	39	Nephrotoxicity: 0% Bone marrow toxicity: 0%
Parghane et al [15]	2021	Total: 9 PCC: 0 PGL: 9	RS	NA	NA: 7	CR: 0% PR: 11% SD: 56% PD: 33% DCR: 67%	Median OS: NR Median PFS: NR	40	Nephrotoxicity: 0% Bone marrow toxicity: 0%
Prado-Wohlwend et al[16]	2022	Total: 9 PCC: 3 PGL: 6	RS	89%	*SDHx* positive: 4 *SDHx* negative: 5	CR: 0% PR: 22% SD: 67% PD: 11% DCR: 89%	Median OS: NA Median PFS: 29	25.6	Nephrotoxicity: 0% Bone marrow toxicity: 11%

 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

Tang et al**[17]	2023	Total: 15 PCC: 3 PGL: 12	RS	80%	*SDHx* positive: 4 *SDHx* negative: 4 NA: 7	CR: 0% PR: 44.4% SD: 33.3% PD: 22.2% DCR: 77.8%	Median OS: NR Median PFS: 25.9§	54	Nephrotoxicity: 7% Bone marrow toxicity: 67%
Our study	2025	Total: 20 PCC: 4 PGL: 16	RS	55%	*SDHx* positive: 11 *SDHx* negative: 6 NA: 3	CR: 0% PR: 5% SD: 60% PD: 35% DCR: 65%	Median OS: NR Median PFS: 24	29	Nephrotoxicity: 0% Bone marrow toxicity: 0%

PCC, phaeochromocytomas; PGL: paragangliomas; PS, prospective study; RS, retrospective study; NA, not available; *SDHx*, Succinate dehydrogenase subunits A-B; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; OS, overall survival; PFS, progression free survival.

*Treated with ^{177}Lu-DOTATATE and capecitabine combined therapy

** Response to treatment was studied in 11 patients out of 15 included in the study.

References:

[1] Kolasinska-Ćwikła A, Pęczkowska M, Ćwikła J, Michałowska I, Pałucki J, Bodei L, et al. A Clinical Efficacy of PRRT in Patients with Advanced, Nonresectable, Paraganglioma-Pheochromocytoma, Related to SDHx Gene Mutation. J Clin Med 2019;8:952. https://doi.org/10.3390/jcm8070952.

[2] Zandee WT, Feelders RA, Smit Duijzentkunst DA, Hofland J, Metselaar RM, Oldenburg RA, et al. Treatment of inoperable or metastatic paragangliomas and pheochromocytomas with peptide receptor radionuclide therapy using 177Lu-DOTATATE. Eur J Endocrinol 2019;181:45–53. https://doi.org/10.1530/EJE-18-0901.

[3] Kong G, Grozinsky-Glasberg S, Hofman MS, Callahan J, Meirovitz A, Maimon O, et al. Efficacy of Peptide Receptor Radionuclide Therapy for Functional Metastatic Paraganglioma and Pheochromocytoma. J Clin Endocrinol Metab 2017;102:3278–87. https://doi.org/10.1210/jc.2017-00816.

[4] Severi S, Bongiovanni A, Ferrara M, Nicolini S, Di Mauro F, Sansovini M, et al. 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 2021;6:100171. https://doi.org/10.1016/j.esmoop.2021.100171.

[5] Jaiswal SK, Sarathi V, Memon SS, Garg R, Malhotra G, Verma P, et al. 177Lu-DOTATATE therapy in metastatic/inoperable pheochromocytoma-paraganglioma. Endocr Connect 2020;9:864–73. https://doi.org/10.1530/EC-20-0292.

[6] Vyakaranam AR, Crona J, Norlén O, Granberg D, Garske-Román U, Sandström M, et al. Favorable Outcome in Patients with Pheochromocytoma and Paraganglioma Treated with 177Lu-DOTATATE. Cancers (Basel) 2019;11:909. https://doi.org/10.3390/cancers11070909.

[7] Nastos K, Cheung VTF, Toumpanakis C, Navalkissoor S, Quigley A-M, Caplin M, et al. Peptide Receptor Radionuclide Treatment and (131)I-MIBG in the management of patients with metastatic/progressive phaeochromocytomas and paragangliomas. J Surg Oncol 2017;115:425–34. https://doi.org/10.1002/jso.24553.

[8] Mitjavila M, Jimenez-Fonseca P, Belló P, Pubul V, Percovich JC, Garcia-Burillo A, et al. Efficacy of [177Lu]Lu-DOTATATE in metastatic neuroendocrine neoplasms of different locations: data from the SEPTRALU study. Eur J Nucl Med Mol Imaging 2023;50:2486–500. https://doi.org/10.1007/s00259-023-06166-8.

[9] Fischer A, Kloos S, Remde H, Dischinger U, Pamporaki C, Timmers HJLM, et al. Responses to systemic therapy in metastatic pheochromocytoma/paraganglioma: a retrospective multicenter cohort study. Eur J Endocrinol 2023;189:546–65. https://doi.org/10.1093/ejendo/lvad146.

[10] Pinato DJ, Black JRM, Ramaswami R, Tan TM, Adjogatse D, Sharma R. Peptide receptor radionuclide therapy for metastatic paragangliomas. Medical Oncology 2016;33:47. https://doi.org/10.1007/s12032-016-0737-9.

[11] Hamiditabar M, Ali M, Roys J, Wolin EM, O'Dorisio TM, Ranganathan D, et al. Peptide Receptor Radionuclide Therapy With 177Lu-Octreotate in Patients With Somatostatin Receptor Expressing Neuroendocrine Tumors. Clin Nucl Med 2017;42:436–43. https://doi.org/10.1097/RLU.0000000000001629.

[12] Demirci E, Kabasakal L, Toklu T, Ocak M, Şahin OE, Alan-Selcuk N, et al. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours including high-grade (WHO G3) neuroendocrine tumours. Nucl Med Commun 2018;39:789–96. https://doi.org/10.1097/MNM.0000000000000874.

[13] Yadav MP, Ballal S, Bal C. Concomitant 177Lu-DOTATATE and capecitabine therapy in malignant paragangliomas. EJNMMI Res 2019;9:13. https://doi.org/10.1186/s13550-019-0484-y.

 Accepted Manuscript published as EO-25-0019. Accepted for publication: 24-Sep-2025

[14] Roll W, Müther M, Sporns PB, Zinnhardt B, Suero Molina E, Seifert R, et al. Somatostatin Receptor–Targeted Radioligand Therapy in Head and Neck Paraganglioma. World Neurosurg 2020;143:e391–9. https://doi.org/10.1016/j.wneu.2020.07.165.

[15] Parghane R V., Talole S, Basu S. 131I-MIBG negative progressive symptomatic metastatic paraganglioma: response and outcome with 177Lu-DOTATATE peptide receptor radionuclide therapy. Ann Nucl Med 2021;35:92–101. https://doi.org/10.1007/s12149-020-01541-z.

[16] Prado-Wohlwend S, Del Olmo-García MI, Bello-Arques P, Merino-Torres JF. [177Lu]Lu-DOTA-TATE and [131I]MIBG Phenotypic Imaging-Based Therapy in Metastatic/Inoperable Pheochromocytomas and Paragangliomas: Comparative Results in a Single Center. Front Endocrinol (Lausanne) 2022;13:778322. https://doi.org/10.3389/fendo.2022.778322.

[17] Tang CYL, Chua WM, Huang HL, Lam WW, Loh LM, Tai D, et al. Safety and efficacy of peptide receptor radionuclide therapy in patients with advanced pheochromocytoma and paraganglioma: A single-institution experience and review of the literature. J Neuroendocrinol 2023;35. https://doi.org/10.1111/jne.13349.