Peptide Receptor Radionuclide Therapy as a Novel Treatment for Metastatic and Invasive Pheochromocytoma and Paraganglioma

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Abstract

At present there is no clinical guideline or standardised protocol for the treatment of metastatic or invasive pheochromocytoma and paraganglioma (collectively known as PPGL) due to the rarity of the disease and the lack of prospective studies or extended national databases. Prognosis is mainly determined by genetic predisposition, tumour burden, rate of disease progression, and location of metastases. For patients with progressive or symptomatic disease that is not amenable to surgery, there are various palliative treatment options available. These include localised therapies including radiotherapy, radiofrequency, or cryoablation, as well as liver-directed therapies for those patients with hepatic metastases (e.g., transarterial chemoembolisation) and systemic therapies including chemotherapy or molecular targeted therapies. There is currently intense research interest in the value of radionuclide therapy for neuroendocrine tumours, including pheochromocytoma and paraganglioma, with either iodine-131 (^{131}I)-radiolabelled metaiodobenzylguanidine or very recently peptide receptor radionuclide therapy

(PRRT), and the most important contemporary clinical studies will be highlighted in this review. The studies to date suggest that PRRT may induce major clinical, biochemical, and radiological changes, with ^{177}Lu -DOTATATE being most efficacious and presenting less toxicity than ^{90}Y -DOTATATE. Newer combination therapies with combined radioisotopes, or combinations with chemotherapeutic agents, also look promising. Given the favourable efficacy, logistic, and safety profiles, we believe that PRRT will probably become the standard treatment for inoperable metastatic PPGL in the near future, but we await data from definitive randomised controlled trials to understand its role.

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Introduction

Metastatic pheochromocytoma (PCC) and paraganglioma (PGL; collectively known as PPGL) is a challenging disease entity as existing therapeutic options are limited. The 5-year overall survival (OS) rate ranges from 34 to 69% [1, 2]. Around 34% of all patients with PPGL will harbour a germline mutation, with succinate dehydrogenase (SDH) subunit B (SDHB; 10.3%), SDHD (8.9%), VHL (7.3%), RET (6.3%), and NF1 (3.3%) being most prevalent [3]. PGL have a higher malignant potential,

with up to 35% of patients being reported to have metastases [4–6] (>40% if SDHB mutation positive [3]). The location of the primary tumour in PGL is often not amenable to complete surgical removal, thus leading to a worse prognosis. A tumour size >5 cm, elevated plasma and/or urine methoxytyramine levels, a pathological Phaeochromocytoma of the Adrenal gland Scaled Score (PASS) >6 for PCCs only, loss of tumoural SDHB staining on immunohistochemistry, and a Ki-67 proliferation index >3%, are other predictive factors for metastatic disease [1]. Traditionally, “malignancy” is operationally defined as the development of metastatic lesions from a PCC or PGL in non-chromaffin tissues, as there are no definitive histopathological criteria for predicting biological aggressiveness in PPGL. However, this terminology is no longer advocated according to the latest 2017 World Health Organisation classification [7]. The most common sites of metastasis are regional lymph nodes, bones, liver and lungs [1]: patients with visceral metastases tend to have a worse prognosis than those with isolated bone disease [8].

The principal management goals in metastatic PPGL are to control symptoms related to catecholamine excess, improve quality of life, prolong survival, and reduce other complications (such as pathological fracture). Debulking or cytoreductive surgery may decrease catecholamine secretion and potentially enhance the efficacy of other therapies [9]; however, the overall value of cytoreductive surgery remains uncertain in the setting of metastatic PPGL due to lack of comparative trials with systemic or locoregional therapies. Interestingly, in a recent retrospective series of 53 patients with PPGL and synchronous metastases, those patients who had resection of the primary tumour had a longer median OS compared to those who did not (85 vs. 36 months, $p < 0.001$), irrespective of other factors such as primary tumour size and location as well as number of metastases [10].

For inoperable cases with progressive or symptomatic disease, there are a variety of localised or systemic palliative treatments available. External beam radiotherapy can be useful for the local control of bone lesions, with symptomatic relief in 94% of the lesions with tumour-related symptoms, and a local control rate of 81% at 5 years in a recent retrospective cohort involving 107 treatment sites in 41 patients [11].

With regards to systemic therapies, conventional chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD) seems to be effective and relatively well-tolerated in the short term, but early relapses are expected [1]. A meta-analysis of four small retrospective studies in-

cluding 50 metastatic PPGL patients treated with CVD revealed complete responses, partial responses and stable disease in 4, 37, and 14% respectively [12]. No improvement in OS was demonstrated in one long-term follow-up study [13], although small series have suggested better response rates in the more aggressive SDHB mutation-related PPGL cohort [2, 14]. Similarly, partial responses to temozolomide have been specifically observed in SDHB-related tumours [15]. In terms of molecular targeted therapy, sunitinib was retrospectively shown to produce clinical benefit concerning tumour size, uptake on ^{18}F -FDG-PET scanning, disease stabilisation and blood pressure control in 17 patients (8 with SDHB mutations) [16], and is currently being explored in the ongoing randomised phase II study, FIRST-MAPPP (NCT01371201). The effectiveness of cabozantinib was evaluated in a small phase II trial; the objective response rate was 45% with a progression-free survival (PFS) of 11 months, while 91% of patients reported clinical benefit [17]. Other potential systemic therapies for SDHx-related PPGL, including the DNA methyl transferase inhibitor guadecitabine (NCT03165721) and PARP inhibitors, are currently under investigation.

Results on Radionuclide Therapy

Conventional ^{131}I -MIBG

Historically, the major radionuclide used in the therapy of PPGLs has been iodine-131 (^{131}I)-radiolabelled metaiodobenzylguanidine (^{131}I -MIBG, also known as iobenguane), principally in use from the 1980s. ^{131}I -MIBG, a high-energy beta-particle-emitting iodinated guanidine analogue structurally comparable to noradrenaline (nor-epinephrine), selectively concentrates in tissues expressing the cell membrane noradrenaline reuptake and vesicular monoamine transporters with high avidity, e.g., tumours of neuroectodermal origin and the sympathoadrenal system [18, 19]. A recent meta-analysis of observational studies, combining the data of 243 patients with metastatic PPGLs treated with ^{131}I -MIBG therapy, showed that 3, 27, and 52% had a complete response, partial response and stable disease, respectively, although there was marked heterogeneity in the response assessment between the studies [20]. In addition, hormonal responses were reported as complete, partial, and stable in 11, 40, and 21%, respectively. These findings are in accord with the conclusion from earlier studies that at least partial tumour responses could be expected in 24–45% of patients after ^{131}I -MIBG therapy [9, 21], with potential anti-hypertensive effects [22].

Fig. 1. A 54-year-old male with SDHB mutation-positive metastatic PCC presenting with right adrenal mass (72 × 59 mm) and skeletal disease who had an ^{123}I -MIBG with SPECT (anterior planar image; **a**), ^{68}Ga -DOTATATE-PET/CT (maximal intensity projection [MIP] image; **b**), and ^{18}F -FDG-PET/CT (MIP image; **c**) performed within 2 months of each other. ^{123}I -MIBG shows a non-avid right adrenal mass with no other sites of disease identified (**a**); ^{68}Ga -DOTATATE-PET/CT (**b**) and ^{18}F -FDG-PET/CT (**c**) identify the large right adrenal mass in addition to multifocal bony metastases, best characterised on ^{68}Ga -DOTATATE-PET/CT. The majority of skeletal disease and the right adrenal mass have intense ^{68}Ga -DOTATATE avidity (greater than background liver), thus making the patient eligible for PRRT. Courtesy of Dr. Shaunak Navalkisoor, Department of Nuclear Medicine, Royal Free Hospital, London, UK, and Dr. Saira Reynolds, Department of Nuclear Medicine, Broomfield Hospital, Chelmsford, UK.

Some authors have suggested that limited sessions of high-dose and multiple low-dose ^{131}I -MIBG treatments are both effective in inducing symptomatic control and disease stabilisation in patients with metastatic PPGL [19]. Although a high-dose regimen (single doses of 18–43 GBq) demonstrated a disease control rate of 69% in a previous phase II study [23], the risk of severe myelosuppression was high, with grade 3/4 neutropaenia and thrombocytopaenia reported in 87 and 83% respectively; 4 patients required autologous haematopoietic stem cell rescue and, concerningly, 2 developed acute myeloid leukaemia during long-term follow-up. Furthermore, the reported 5-year OS rate (64%) was similar to conventional-dose ^{131}I -MIBG studies [24].

Hypothyroidism is another well-known side effect, and therefore the use of potassium iodide for protection of the thyroid gland is required in the peri-procedural period. Other adverse events include hypertension, gastrointestinal upset, liver toxicity, renal impairment, and gonadal failure, warranting close monitoring and regular long-term follow-up [9, 24, 25]. Certain medications that interfere with MIBG uptake such as labetalol, calcium channel blockers, tricyclic antidepressants, sympathomimetic amines (phenylephrine, ephedrine), and serotonin-noradrenaline reuptake inhibitors may need to be withdrawn prior to treatment to optimise uptake. The long

duration of isolation after radiation exposure is also a drawback of conventional ^{131}I -MIBG therapy [9, 19].

High-Specific Activity ^{131}I -MIBG

Very recently, the FDA has approved Azedra® (Progenics Pharmaceuticals), a high-specific-activity preparation of ^{131}I -MIBG, as the first and only approved therapy for patients over 12 years old with MIBG-avid, unresectable, locally advanced or metastatic PPGL. As the transporter mechanisms on which MIBG action relies are a saturable pathway, theoretically high-specific-activity labelling should allow for greater uptake and retention of the radiopharmaceutical. The FDA approval was based on the data from a pivotal phase II open-label, multicentre trial in which 68 patients with MIBG-positive metastatic PPGL, who were not candidates for curative surgery, received one or two therapeutic doses of Azedra®: 25% of the patients reached the primary endpoint of ≥50% reduction of all blood pressure-lowering medications for at least 6 months, while 23 and 69% achieved a partial response and stable disease, respectively, by response evaluation criteria in solid tumours (RECIST), constituting a disease control rate of 92% [26]. The median OS was 37 months and the most frequent (≥50%) treatment-emergent adverse events were bone marrow suppression, nausea, and fatigue.

Fig. 2. Recurrent PCC following resection of primary in a 58-year-old male (PPGL susceptibility gene testing normal). Maximal intensity projection (MIP) and coronal images show extensive ^{68}Ga -DOTATATE avid disease in liver, lung, nodes, and bone, with significant disease progression at baseline (a), 6 months (b), and 12 months (c) despite treatment. Courtesy of Dr Shaunak Navalkissoor, Department of Nuclear Medicine, Royal Free Hospital, London, UK.

Peptide Receptor Radionuclide Therapy

Sufficient lesion avidity on ^{123}I -MIBG scintigraphy is an important prerequisite for therapeutic ^{131}I -MIBG. Although ^{123}I -MIBG scanning has a sensitivity of around 90% in detecting PPGL in general, this drops to <80% for metastatic lesions [1, 27] and even lower (<50%) for SDHx-associated tumours and head-and-neck PGLs (HNPPGL) [1]; this is due to reduced expression of nor-epinephrine transporters in these mutations, indicating inadequate MIBG avidity in these conditions and ruling out MIBG therapy in many cases. Peptide receptor radionuclide therapy (PRRT), using radiolabelled somatostatin analogues, may serve as an appealing and possibly preferable alternative [28]. In fact, the majority of PPGL, like other neuroendocrine tumours (NETs), strongly express somatostatin receptors (SSTRs) of high affinity and specificity [29–31], with the most common subtypes being 2a and 3 [32, 33]. Indeed, many metastatic PPGL demonstrate high uptake on SSTR-based scans but not on ^{123}I -MIBG scintigraphy [34–36]. It has also been observed that SDHx-deficient tumour cells exhibit much stronger SSTR immunostaining when compared to SDHx-sufficient tumours [37, 38]. Several other studies have illustrated the diagnostic superiority of SSTR-based imaging for patients with SDHB mutations and HNPPGLs [39–42], and also MEN2-associated metastatic PCC [43], due to some degree of functional dedifferentiation in these more aggressive tumours [18]. ^{68}Ga -DOTA-somatostatin analogue-PET scanning was shown to

be the best diagnostic imaging modality for metastatic PPGL, with significantly higher sensitivity (92–100%) and greater lesion-to-background contrast when compared to ^{123}I -MIBG scintigraphy, ^{18}F -DOPA-PET, or ^{18}F -FDG-PET [3, 36, 42, 44, 45], and thus should be considered as the investigation of choice to identify disease extent (Fig. 1), although with the caveat that small PCC may be difficult to distinguish against normal adrenal uptake and adjacent renal uptake. Of all modern SSTR-based imaging techniques, ^{68}Ga -DOTATATE-PET scanning is most favoured as it has the greatest affinity for SSTR type 2 [30] (Fig. 2). Although unlabelled “cold” somatostatin analogues have been notably successful for gastroenteropancreatic NETs, these have been unsuccessful in the control of the hormonal syndrome in metastatic PPGLs [9]. A well-designed study involving 10 patients with PCC failed to demonstrate efficacy of monthly intramuscular octreotide in symptomatic or hormonal control [46]. This may possibly be explained by the speculation that metastatic PCCs, as opposed to metastatic PGLs, are mostly SSTR type 2 negative [47]. This may also relate to the fact that octreotide lacks affinity for SSTR type 3 and newer multiligand agents such as pasireotide may theoretically be more effective [33, 48, 49], but this concept has not as yet been tested.

There is a growing body of evidence that PRRT using high-energy beta-particle-emitting radionuclides such as ^{90}Y -DOTATOC and ^{177}Lu -DOTATATE (Fig. 3) is highly effective in the treatment of NETs in terms of objective

Fig. 3. A 28-year-old female with head and neck PGL (SDHB mutation-positive and variant of unknown significance in SDHD gene; primary tumour resected) metastatic to lung and bone with ^{68}Ga -DOTATATE avidity. ^{68}Ga -DOTATATE maximal intensity projection (MIP) image before treatment (**a**); she was treated with PRRT (^{177}Lu -DOTATATE), and anterior view (**b**) and posterior view (**c**) of the whole body post-treatment scans show a similar distribution of radioisotope uptake. Courtesy of Dr Shaunak Navalkissoor, Department of Nuclear Medicine, Royal Free Hospital, London, UK.

tumour response, disease stabilisation, symptomatic control, and preservation of quality of life, while maintaining a favourable safety profile [50–52]. This was specifically demonstrated in the phase III randomised controlled trial *NETTER-1*, in which treatment with ^{177}Lu -DOTATATE resulted in a significantly longer PFS and a higher objective response rate when compared to high-dose octreotide LAR among patients who had metastatic midgut NETs [50]. There was a 79% reduction in the risk of disease progression or death with ^{177}Lu -DOTATATE ($p < 0.001$). In light of these impressive findings, the FDA has approved Lutathera® (^{177}Lu -DOTATATE) for the treatment of SSTR-expressing gastroenteropancreatic NETs in adults, while in the UK the National Institute for Health and Care Excellence (NICE) has assessed PRRT as cost-effective for the treatment of this subgroup of NETs.

Around a decade ago, some centres first reported their experience in using PRRT for metastatic PPGL. In a cohort of 20 patients with metastatic NETs, Frilling et al. [53] illustrated a case of an unresectable metastatic HNPPGL showing a partial response after ^{90}Y -DOTATOC and ^{177}Lu -DOTATOC treatments. In another case series, 12 patients with PGL (75% metastatic) received ^{177}Lu -DOTATATE; of the 4 patients who had evidence of disease progression at baseline, 2 demonstrated tumour regression and 1 stable disease after treatment, whereas more than half of the remaining patients had stable disease after a median follow-up of 13 months [54]. Later, in

a retrospective phase II study, Forrer et al. [34] described 28 metastatic PPGL with radiological progression at baseline (9 PCCs, 19 PGLs) showing long-lasting partial remissions after ^{90}Y -DOTATOC (3 combined with ^{177}Lu -DOTATOC), with only limited and tolerable toxicities. Partial remissions, minor responses, and stable disease were observed in 2, 5, and 13 patients, respectively, at the time of restaging. These effects were quite durable with a mean duration of 18 ± 14 months, with the two partial remissions lasting 23 and 41 months, respectively. However, it is worth noting that the tumour characteristics, imaging, and treatment protocols involved in these studies were heterogeneous due to their retrospective nature, and the subjects had undergone various treatment modalities before PRRT. Subsequently, the only prospective phase II clinical trial was conducted in a single centre to examine the efficacy and safety profile of ^{90}Y -DOTATOC, recruiting 1,109 patients with metastatic NETs, including 11 PCCs and 28 PGLs [55]. All patients had disease progression before study entry. Radiographic, biochemical, and clinical responses were observed in 36.4, 18.2, and 45.5%, respectively, in the PCC group, and 10.7, 14.3, and 21.4%, respectively, among the PGL patients. The PCC and PGL groups had a mean OS of 32 and 82 months, respectively. Another important finding in this large cohort was that tumour uptake on the initial molecular imaging correlated with OS (HR 0.45, $p < 0.01$). Overall, there were 142 patients (12.8%) showing tran-

sient grade 3–4 myelosuppression, while 102 patients (9.2%) had severe permanent renal toxicity.

More recently published papers have further explored the use of PRRT in patients with surgically incurable disease associated with SDHx mutations and HNPGLs. Zovato et al. [56] studied 4 female SDHD carriers with biochemically silent, non-metastatic carotid body or thoracic PGL, considered inoperable due to the tumour size or location, who later developed disease progression and received 3–5 cycles of ^{177}Lu -DOTATATE. Two showed a partial response by RECIST while the other 2 had stable disease with reduced tumour uptake on subsequent scintigraphy. Another case report described a patient carrying an SDHD mutation with a history of a resected cervical PGL presenting with histologically proven bone and liver metastases, strongly avid on ^{68}Ga -DOTATOC-PET/CT but with negative ^{124}I -MIBG-PET/CT scanning [57]. These lesions showed minor responses after two cycles of ^{90}Y -DOTATOC. Pinato et al. [28] examined the efficacy of ^{177}Lu -DOTATATE in 5 young patients with aggressive, metastatic SDHB-related intra-abdominal PGL, all with bone metastases and catecholamine excess: 3 patients with metastatic relapse after prior excision achieved stabilisation following PRRT, 1 had a partial response, while 1 patient progressed. The median PFS was 17 months while the median OS was not reached. Another case series reported 9 patients with unresectable HNPGL, either due to critical tumour location or multifocal involvement, undergoing ^{90}Y -DOTATATE PRRT (4 in combination with ^{177}Lu -DOTATATE) [58]. It is unclear whether these cases had progressive or stable disease at baseline. After PRRT, all patients had stable disease by RECIST. Of the two-thirds presenting with symptoms related to cranial nerve or bone involvement, symptomatic improvement after treatment correlated with the imaging response in 4 cases. Only 1 patient had distant metastases (rib, vertebra, and lung) before PRRT, and there was marked reduction in SUV_{max} from 27.6 to 5.4 in the spinal lesions after treatment, in concordance with the resolution of back pain. Another patient had resolution of tinnitus due to reduction in tumour size. Remarkable improvements were also seen in the case of a young man with a recurrent unresectable carotid body PGL, as reported by Gupta et al. [59]: he had a response at the primary site and total disappearance in the nodal and T7 vertebral metastases after five cycles of ^{177}Lu -DOTATATE. Cecchin et al. [60] also described a patient aged in his thirties presenting with multifocal non-secretory PGL without a known germline mutation who underwent PRRT after presenting with worsening symptoms of spi-

nal cord compression due to progressive spinal disease. His symptoms subsided with a $70 \pm 13.0\%$ mean volume reduction in his 23 spinal lesions on post-treatment MRI scans; the mean SUV_{max} reduction in 17 lesions was $85 \pm 13.3\%$ (5 were no longer visible) on ^{68}Ga -DOTANOC-PET/CT transaxial images. In a retrospective study concerning 14 patients with HNPGLs who underwent three cycles of ^{177}Lu -DOTATATE, Estêvão et al. [61] found that patients with jugulotympanic PGLs achieved better treatment outcomes than those with carotid body lesions in terms of symptoms and SUV on ^{68}Ga -DOTANOC-PET/CT, and the initial tumour SUV actually predicted the subsequent response to PRRT ($R = +0.64$, $p = 0.014$). None of the patients suffered from major treatment-related adverse events in the above studies. It is also of some interest that responsivity to ^{177}Lu -DOTATATE may be demonstrated using functional biochemical assessment; using proton-1 magnetic resonance spectroscopy (^1H -MRS), Casey et al. [62] have recently shown that there was a loss of the succinate peak, a metabolic marker of the SDH enzymatic defect, after 4 cycles of ^{177}Lu -DOTATATE treatment in a single case, although the significance of this change on future prognosis is unclear.

A recent retrospective analysis focused on the potential effects on clinical, biochemical, and tumour responses, and survival benefits of PRRT in 20 patients (mutation status: 7 SDHB, 1 SDHD, 2 negative, 10 unknown; primary location: 8 PCC, 12 PGL) having either uncontrolled hypertension due to functional PPGL or non-functional progressive metastatic disease or recurrence [35]: 80% of these patients (16/20) had not received prior systemic therapy. One to four courses of ^{177}Lu -DOTATATE PRRT were administered with a median cumulative dose of 22 GBq. Nine patients received radiosensitising chemotherapy with 5-fluorouracil and/or temozolomide. At 3 months after treatment, 8/13 patients (62%) with refractory secondary hypertension were able to reduce the dose of anti-hypertensive medications, 8/13 reported symptomatic benefit, and 4/7 who had elevated plasma metanephrine/normetanephrine measurements showed reduced levels; 86% (12/14) had serial declines in chromogranin A. Of those with sufficient data, 47, 41, and 12%, and 36, 50, and 14%, had an imaging response, stable findings or progressive disease on post-treatment ^{68}Ga -DOTATATE-PET/CT ($n = 17$) and CT scans ($n = 14$), respectively. The median PFS was 39 months while the median OS was not reached (median follow-up, 28 months). It is, however, important to note that the treatment indication for the majority of the study cohort was uncontrolled secondary hypertension rather than radio-

logical disease progression. The most common toxicities were grade 2–3 lymphopaenia and thrombocytopaenia. Symptoms of acute catecholamine release developed 3 h after ^{177}Lu -DOTATATE administration in 1 patient without adequate alpha-adrenoceptor blockade and with a possible contribution from dexamethasone premedication. Another patient died of unexplained cardiac arrest shortly after the third cycle of PRRT.

These results, albeit in small series and case reports with heterogeneous patient groups and treatment outcome measurements, clearly demonstrate that PRRT is a strikingly promising treatment option for metastatic as well as localised but inoperable PPGL, with substantial tumour responses and symptomatic relief, and minimal toxicity. Responses are seen in patients with multiple lesions, SDHB/D mutations and bone involvement, irrespective of the primary tumour location.

Comparative Radionuclide Studies

To date, very few studies have compared the performances of different radiopharmaceutical agents in the treatment of PPGLs. In a recent retrospective study conducted at our centre, PRRT appeared to produce a better treatment response and greater survival benefit but comparable side-effect profiles when compared to ^{131}I -MIBG therapy [63]. In this cohort comprising 22 patients with progressive, metastatic PPGLs (7 PCC and 15 PGL, 5 SDHB-related), 9 received PRRT (8 ^{90}Y -DOTATATE, 1 ^{177}Lu -DOTATATE), 11 ^{131}I -MIBG, and 2 a combination of the above. A total of 30 treatment cycles were administered; 9 treatments (8 ^{131}I -MIBG, 1 PRRT) to the PCC group and 21 treatments (8 ^{131}I -MIBG, 13 PRRT) to the PGL group. Most PCCs were treated with ^{131}I -MIBG due to reasonable uptake on MIBG scans, whereas PGLs were treated with either ^{131}I -MIBG or PRRT based on their increased avidity on SSTR-based imaging. Considering all patients in the study cohort, PRRT demonstrated higher rates of disease stabilisation (as per RECIST assessment) when compared to ^{131}I -MIBG (13/13 vs. 10/16, $p = 0.013$), but there was no significant difference in either mean OS (60.8 ± 11.1 vs. 41.2 ± 10.4 months, $p = 0.09$) or mean PFS (38.5 ± 9.4 vs. 20.6 ± 3.4 months, $p = 0.10$). However, when the treatment outcome data regarding ^{131}I -MIBG and PRRT were further stratified according to tumour type, there was a significant difference in OS and PFS in the PGL group in favour of PRRT (22.8 ± 6.3 vs. 60.8 ± 11.1 months, $p = 0.012$, and 14.4 ± 2.9 vs. 38.5 ± 9.4 months, $p = 0.018$, respectively). The rate of disease stabilisation in the PRRT arm was also superior to ^{131}I -MIBG in the PGL cohort (13/13 vs. 4/8, $p = 0.005$). These results suggest that

PGL may show improved outcomes with PRRT compared with ^{131}I -MIBG. There has indeed been speculation that PCC and PGL may each display different biological and biochemical characteristics, with metastatic PGLs having much higher affinity for SSTR type 2 than metastatic PCCs [47]. However, given the small number of patients with PCC receiving PRRT in this study, no conclusions could be drawn. Moreover, half of the patients (11/22) had additional systemic therapies such as CVD chemotherapy and somatostatin analogues, confounding the effects of PRRT. More carefully designed and balanced, larger-scale prospective trials are therefore required before such conclusions can be definitively drawn. There were no major differences in toxicities between the two treatment arms. While there is a much longer experience with “conventional” ^{131}I -MIBG and renal toxicity may be less frequent [19], PRRT has the potential benefits of producing fewer haematological side effects and does not require pre-treatment thyroid blockade [35]. However, the choice must also be governed by tracer concentration in tumour lesions in the respective nuclear imaging modalities [35].

DOTATATE is currently the most widely used DOTA-conjugated somatostatin analogue for PRRT as it binds with 6- to 9-fold greater affinity to SSTR type 2 compared with DOTATOC [64, 65]. Based on the current literature, ^{177}Lu -DOTA-somatostatin analogue-PRRT has at least similar efficacy in the treatment of various NETs when compared to ^{90}Y [66], but its toxicity profile is much more favourable in terms of myelosuppression and nephrotoxicity [17, 66–68]. ^{177}Lu emits beta particles with a shorter range, lower energy but longer half-life when compared to ^{90}Y , and it also emits gamma radiation which allows post-treatment monitoring of tumour uptake and dosimetry [64, 65]. To date, there is no study specifically comparing the efficacy of these two radionuclides in the treatment of PPGLs. Nevertheless, given their different radiobiological properties, some researchers have evaluated the clinical outcomes of combination therapy [69, 70]. Prasad et al. [71] retrospectively analysed three different treatment regimens among 20 patients with metastatic PPGL (7 ^{90}Y -DOTATATE, 5 ^{177}Lu -DOTATATE, 8 sequential combination of the two) and found that the response rate was highest (50%) in the combination group (vs. 14 and 20% in the ^{90}Y and ^{177}Lu group, respectively): 29% (2/7) and 57% (4/7) had stable lesions and progressive disease, respectively, in the ^{90}Y group, as compared to 60% (3/5) and 20% (1/5), respectively, in the ^{177}Lu group. However, this study is small and observational, and few data are available on their methods or toxicity. Larger prospective studies are required to

Table 1. Summary of the findings of the major studies on PRRT in PPGL

Ref.	n	Age, years (mean)	Mutation status	Location of primary tumour	Disease status at baseline	With mets, n	With PRRT as first-line Tx ^a , n	Radioisotope (dose)	FU, months (mean)	Radiographic response, % of patients			Other major treatment outcomes
										PD	SD	MR/PR	
28	5	16–47 (34)	SDHB	Abd	NS	5	3	¹⁷⁷ Lu (6.6–7.6 GBq ^f , 1–4 cycles)	NS	20	60	20	Median PFS 17 (0–78) months; mean OS 53 months (median OS was not reached)
34	28	16–69 (42)	NS	9 PCC 19 PGL	All PD	28	18	⁹⁰ Y (200 mCi/m ² body surface ^f); 3 combined with ¹⁷⁷ Lu	6–50 (19)	28.6	46.4	25	TTP was 3 to >42 months; the responses were durable with a mean duration of 18±14 (6–44) months
35	20	21–77	7 SDHB 1 SDHD 2 None 10 Unkn.	8 Adrenal 5 HN 5 Abd 2 HN+Abd	5 PD 14 SD ^c 1 Unkn.	20	16	⁷⁷ Lu (median: 22 GBq ^f); 9 combined with radiosensitising chemotherapy	5–74 (28 ^a)	14	50	36	Median PFS 39 months; median OS was not reached; 8/13 and 8/13 patients had reduced doses of anti-HT drugs and improvement in hormone-related symptoms, respectively; more than half had >50% CgA and >25% decrease in MN/MN ^b
54	12	22–55 (40)	NS	1 Adrenal 5 HN 6 Others	4 PD 5 SD 3 Unkn.	9	8	¹⁷⁷ Lu (14.8–29.6 GBq ^f)	4–30 (13 ^a)	25	50	16.7	TTP 11 and 15 months in 2 patients, respectively; median TTP in patients with PGL was not reached
55	39	11–91 (59 ^a) ^b	NS	11 PCC 28 PGL	All PD	39	NS	⁹⁰ Y (NS)	NS	NS	NS	47	Mean OS in the PCC and PGL groups was 32 and 82 months, respectively; 32.5 and 66.9% of patients had a biochemical and clinical response, respectively
56	4	41–74 (56)	SDHD	2 HN 2 Thoracic	All PD	0	3	¹⁷⁷ Lu (11.5–27.8 GBq ^f)	12–25 (16)	0	50	50	–
58	9	30–75 (52)	NS	HN	NS	1	9	⁹⁰ Y (1.5–5.7 GBq ^f , 2–4 cycles); 4 combined with ¹⁷⁷ Lu (5.4–7.5 GBq ^f)	4–80 (18)	0	100	0	4/9 and 5/9 patients had partial molecular response and stable disease, respectively, based on EORTC criteria; in 4/6 symptomatic patients, molecular responses correlated with a symptomatic improvement
63	22	7–71 (47)	5 SDHB 17 None	7 PCC 15 PGL	All PD	10	11	11 ¹³¹ I-MIBG (3.2–66.4 GBq ^f); 8 ⁹⁰ Y (3.6–17.7 GBq ^f)/1 ¹⁷⁷ Lu (NS); 2 combination of the two	2–134	MIBG: 37.5 PRRT: 0	MIBG: 62.5 PRRT: 100	–	Of the entire cohort, the mean OS/PFS in the ¹³¹ I-MIBG and PRRT arms were 41.2/20.6 months and 60.8/38.5 months, respectively, <i>p</i> = 0.09/0.10; in the PGL subcohort, OS and PFS in the ¹³¹ I-MIBG and PRRT arms were 22.8/60.8 months and 14.4/38.5 months, respectively, <i>p</i> = 0.012/0.018
71	20	(54)	NS	NS	NS	20	NS	⁷ 90Y (2.3–3.6 GBq ^f , 1–6 cycles); 5 ¹⁷⁷ Lu (2.7–7.0 GBq ^f); 8 combination of the two	NS	NS (41.7 ^b)	NS (41.7 ^b)	30	The combination group achieved the highest response rate (50%) among the three groups

Abd, abdomen; CgA, chromogranin A; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; FU, follow-up; HN, head and neck; HT, hypertension; mets, presence of distant metastases before radioisotope therapy; MN, plasma metanephrines; MR, minor response; n, number of subjects with PPGL; MN, plasma normetanephrines; NS, not specified; OS, overall survival; PCC, pheochromocytoma; PD, progressive disease; PGL, paraganglioma; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression; Tx, treatment; Unkn., unknown.

^a Median value instead of mean.

^b Based on the data from the whole cohort of patients with neuroendocrine tumours.

^c Indication for PRRT was either uncontrolled secondary hypertension in these 14 patients, or non-functional progressive metastatic disease or local recurrence in the remaining 6 patients.

^d Number of patients having PRRT as first line systemic treatment, i.e., those treated with prior surgical resection, embolisation, or external beam radiotherapy were also included.

^e Radioisotope dose per cycle of the respective radioisotope therapy.

^f Cumulative radioisotope dose of the respective radioisotope therapy.

^g Based on the data from the ⁹⁰Y-only and ¹⁷⁷Lu-only groups.

^h Based on the data from the 14 and 7 patients with serial CgA and plasma MN/MN measurements, respectively.

address this issue, which will need to consider cost, toxicity, and the accessibility of both types of radionuclide.

It is also unclear as to whether PRRT can be safely and effectively combined with radiosensitisers or chemotherapeutics [35, 72, 73]. The use of combinations of radiopharmaceuticals could also be explored for mixed SSTR- and MIBG-avid lesions to allow possible synergistic effects and delivery of higher radiation doses to the respective target tissues with differential side effects [49]. Current advances in PRRT for NETs such as the use of radiolabelled SSTR antagonists, which are more readily bound to target cells [74], and high-energy α -particle emitters, may also be considered [75–77]. The findings of the major studies concerning the use of PRRT in PPGL are summarised in Table 1.

Toxicity Concerns

PRRT is usually well tolerated: a phase I study demonstrated the safety of PRRT co-administered with amino-acid infusion in 17 children and younger adults (1 PGL) [78]. Besides the known toxicity profile including fatigue, myelosuppression, and nephrotoxicity, a hormonal crisis precipitated by radionuclide therapy is a genuine concern in PPGL, as observed in a patient with a metastatic PCC who developed hypotension and myocardial ischaemia 1 day after ^{177}Lu -DOTATATE therapy [79]. Makis et al. [80] also described 2 patients who developed an acute catecholamine crisis within hours and 3 days after treatment, respectively. We have also had experience of a catecholamine crisis in a patient with metastatic PCC during treatment with ^{131}I -MIBG. Special precautions including adequate alpha-adrenoceptor blockade and close monitoring are mandatory when treating PPGL with PRRT, especially for syndromic patients [35], and this has also been our experience. It is possible that withholding glucocorticoid premedication [35] or lengthening the radioisotope infusion time and/or decreasing the initial treatment dose [80], may be helpful in preventing hypertensive crises. Certainly, close attention needs to be paid to fluctuations in blood-pressure control following each treatment. Pulmonary toxicity and intense pain related to reactive tumour swelling have also been reported [28].

Limitations

Some limitations of this review are recognised. As most of the available studies are small and retrospective in nature, the data provided are highly heterogeneous in terms of the clinical question of interest, patient population, study design and methodology, and treatment protocol. In addition, the definitions of tumour response

(clinical, biochemical, radiological) and other parameters for survival analysis are inconsistent between the studies, rendering interpretation and comparison more difficult.

There were a wide range of indications for PRRT in these studies, such as presence of metastatic disease, prior disease progression, critical tumour location, uncontrolled hypertension, or a combination of the above. However, the treatment outcome may be variable in these patient groups. While many of the quoted studies principally included patients with metastatic lesions [28, 34, 35, 54, 55, 71], cases with non-metastatic PPGL were also reported in this review, comprising around 17% of the patients listed in Table 1. This may limit the overall interpretation of the potential efficacy of PRRT. Some studies predominantly included patients with progressive disease at baseline [34, 55, 56, 63], the target subgroup of patients who warrant further prospective research. However, a number of patients reported in this review had stable disease at study entry (Table 1), and such information was either unknown or lacking in the remaining cases. Of the 93 patients who had documented progressive disease prior to PRRT, a radiological tumour response was observed in 25–50% [34, 54–56] with disease stabilisation in 71.4–100% [34, 35, 54, 56, 63]. However, we are unable to extrapolate these results to the rest of the study population.

It would be worthwhile to explore the role of PRRT as first-line treatment in progressive, metastatic PPGL. However, in the studies we reviewed, some subjects had undergone different treatment modalities prior to PRRT (Table 1), and we could not obtain specific outcome data in patients who had been treated with PRRT in the first-line setting.

We have been unable to provide sufficient evidence to demonstrate the possible difference in post-PRRT outcomes among various tumour subtypes (e.g., PCC vs. PGL) and different radionuclides (^{131}I -MIBG vs. ^{90}Y -DOTA-TOC/TATE vs. ^{177}Lu -DOTA-TOC/TATE, alone or in combination) due to the very limited number of comparative studies. Further prospective clinical trials involving larger numbers of patients with metastatic PPGL should be able to explore these factors in more detail.

Conclusions

Although we believe there is an emerging role for PRRT in treating SSTR-positive metastatic PPGL, there are still many unanswered questions concerning the most appropriate therapeutic approach. Considering its favourable treatment outcome with minimal toxicity con-

cern, and with the increasing availability of more effective and practical radionuclide agents, PRRT in its current or future guises looks to play a leading role in the therapy of these tumours; however, phase III randomised controlled trials are required to definitively establish the role of PRRT in the treatment of these very difficult cases. The role of newer targeted anti-oncogenic agents, alone and in combination, also needs to be taken into account in treating these complex tumours [81, 82].

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors see and manage patients with PPGL receiving PRRT. The first draft was written by the corresponding author while all authors contributed to writing and commenting on the final report.

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