Treatment of inoperable or metastatic paragangliomas and pheochromocytomas with peptide receptor radionuclide therapy using ^{177}Lu-DOTATATE

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ABSTRACT

Objectives: Inoperable or metastatic paragangliomas (PGL) and malignant pheochromocytomas (PCC) are rare tumours with limited options for systemic treatment. Aim of this study was to assess the safety and efficacy of the radiolabelled somatostatin analogue [^{177}LutetiumDOTA^{0}-Tyr^{3}]octreotate (^{177}Lu-DOTATATE) for the treatment of PGLs and PCCs.

Methods: Patients with histologically proven inoperable or malignant PGLs and PCCs treated with ^{177}Lu-DOTATATE at our centre were retrospectively analysed. Patients were treated with up to four cycles of ^{177}Lu-DOTATATE with an intended dose of 7.4 Gb per cycle. Response was assessed with use of RECIST 1.1

Results: Thirty patients were included: 17 with parasympathetic, 10 with sympathetic PGLs and 3 with PCCs. Grade 3/4 subacute haematotoxicity occurred in 6 (20%) of patients. A reversible subacute adverse event due to cardiac failure following possible catecholamine release occurred in two patients. Best tumour response was partial response in 7 (23%) and stable disease in 20 (67%), whereas 3 (10%) patients had progressive disease. In 20 patients with baseline disease progression, tumour control was observed in 17 (85%); the median progression free survival was 91 months in patients with parasympathetic PGLs, 13 months in patients with sympathetic PGLs and 10 months in patients with metastatic PCCs.

Conclusion: This study suggests that PRRT with 177Lu-DOTATATE is a safe and effective treatment option for patients with inoperable or malignant PGL and PCC.

INTRODUCTION

Paragangliomas (PGLs) are rare tumours that arise from the chromaffin cells of the neural crest-derived sympathetic and parasympathetic paraganglia. Sympathetic paraganglia are located from the superior cervical ganglion down to the pelvis and are predominantly found in the abdomen.[1] Lesions originating specifically from the adrenal medulla are called pheochromocytomas (PCCs). Parasympathetic PGLs are found in the head and neck region, by originating from the carotid bodies, and the jugulotympanic and vagal paraganglia. In recent years an increasing numbers of genetic mutations have been identified that predispose for PGLs and PCCs, in particular in the genes encoding succinate dehydrogenase (SDH).[2,3] The subtype B (SDHB) mutation is primarily associated with sympathetic PGLs and carries a high risk of malignancy, whereas the subtype D (SDHD) mutation is mostly associated with multiple parasympathetic head and neck PGLs.[4]

Predominantly sympathetic but also parasympathetic PGLs can present with clinical symptoms due to catecholamine hypersecretion.[5] In case of secretory PGLs and PCCs, treatment can be complicated by excess (nor)epinephrine/(nor)adrenaline release during interventions. Therefore, patients should be carefully monitored and receive adequate (pre-)treatment with alpha-adrenergic receptor blockade.[6] Independent of hormonal status, PGLs and PCCs are considered malignant if there are regional or distant metastases.[6] Sympathetic PGLs are more likely to be hormonally active and often show distant metastatic spread, whereas parasympathetic PGLs often present with local swelling and neurological signs due to local extent of disease.[5,7] For localised disease, surgery is the treatment of first choice. In metastatic disease, treatment options are limited and prognosis is usually poor; the reported 5-year survival rate of metastatic PGLs is between 34% and 60%.[8]

PGLs and PCCs are known to express high levels of somatostatin receptor (SSTR) subtypes, in particular subtype 2, on their cell surface, similar to other neuroendocrine tumours (NETs).[9,10] These receptors can be targeted for imaging and treatment of the tumours using radiolabelled somatostatin analogues (SSAs). This technique has been established as a successful treatment for gastroenteropancreatic NETs, but can be more widely applied for other tumours expressing high affinity SSTRs[11-13]. The efficacy of peptide receptor radionuclide therapy (PRRT) with [^{177}Lutetium-DOTA^{0}-Tyr^{3}]octreotate (^{177}Lu-DOTATATE) is dependent on adequate SSTR subtype 2 expression, which is usually assessed by planar scintigraphy with single photon emission computed tomography (SPECT) or positron emission tomography (PET) using radiolabelled SSAs.[14,15] In clinical practice, many patients with PGLs have been treated with surgery, chemotherapy and/or ^{131}Iodine-metaiodobenzylguanidine (^{131}I-MIBG) at the time of assessment for PRRT. Patients with metastatic PCCs usually undergo resection of the primary tumour and subsequent therapy with ^{131}I-MIBG for the metastases.[16] In these settings, but perhaps also at an earlier stage, PRRT may be considered as a (salvage) treatment. There is limited experience with PRRT in PGLs and metastatic PCCs, but recent

evidence suggests a favourable effect of PRRT at limited toxicity advocating consideration of radiolabelled SSAs in the treatment algorithm for these tumours.[17] This paper reports on the single-institution experience with the treatment of PGLs and metastatic PCCs using ^{177}Lu-DOTATATE.

METHODS

Patients

This is a retrospective case series of patients with PGLs and PCCs treated with PRRT at the department of Radiology & Nuclear Medicine at the Erasmus University Medical Centre Rotterdam, the Netherlands, starting from January 2000. The study was approved by medical ethical review board of the Erasmus Medical Center and written informed consent was obtained from all participants. Inclusion criteria for this cohort were adequate tumour SSTR expression (uptake equal to (grade 2) or greater than normal liver tissue (grade 3) or greater than kidneys/spleen (grade 4)) as evaluated on planar scintigraphy with ^{111}In-DPTA-octreotide SPECT, haemoglobin $\geq$ 5.5 mmol/L, white blood cell count $\geq$ 2x10^9/L, platelet count $\geq$ 75x10^9/L, creatinine clearance $\geq$ 40 mL/min (assessed in 2x 24-hour urine collection) and Karnofsky performance status $\geq$ 50. From this cohort, all patients with histologically proven inoperable or metastatic PGLs and patients with metastatic PCCs were considered, if treated with at least 1 cycle of PRRT with ^{177}Lu-DOTATATE. Patients were treated for indications as radiological progression, symptomology or high tumour burden. For inclusion a follow-up of more than 1 year after the last therapy cycle was required. Foreign patients and patients without at least 1 response evaluation were excluded. Baseline radiological progression was defined as any growth or new lesions on radiological imaging (CT/MRI) or new lesions on nuclear imaging (MIBG/SSTR-imaging)

Treatment

^{177}Lu-DOTATATE was prepared and administered as described earlier.[13,18] Standard treatment consisted of 4 cycles of PRRT with a dose of 7.4GBq per cycle, up to an intended cumulative dose of 29.6 GBq with intervals of 6-12 weeks between cycles. Patients with elevated catecholamine production were pre-treated with alpha- and, if indicated, beta-adrenergic receptor blockers.

Outcome Measurements and Analysis

Routine haematology, liver and kidney function tests and quality of life measurement were performed at baseline, 4-6 weeks after every treatment and at follow-up visits. Follow-up imaging was performed at 3 and 6 months after the last treatment, and every 6 months thereafter. Toxicity was graded based on the Common Terminology Criteria for Adverse

Events version 3.0, radiographic tumour assessment was performed according to the response evaluation criteria in solid tumours (RECIST) 1.1.[19] Primary events are defined as progressive disease (PD) according to RECIST, start of another treatment or death. Progression free survival (PFS) was defined as time from the start of PRRT until primary event or last radiographic outcome measurement. Overall survival (OS) was defined as time from the start of PRRT until death or the last clinical follow–up. Kaplan-Meier survival analysis was used to express survival corrected for differences in follow-up. All statistics were performed with SPSS version 23.0 (Armonk, NY: IBM Corp). A p-value of smaller than 0.05 was considered statistically significant.

RESULTS

Thirty patients were included of which 17 patients with parasympathetic PGLs, 10 with sympathetic PGLs, and 3 patients with metastatic PCCs. At baseline 17 (57%) patients had metastatic disease and 13 (43%) patients has localised disease of which 9 (69%) patients had a PGL with multiple localisations. SDHB mutations were confirmed in 5 out of 10 patients (50%) with sympathetic PGLs and SDHD mutations were confirmed in 11 (65%) patients with parasympathetic PGL. Previous therapies included surgery (63%) and external beam radiotherapy (20%). Eight patients (27%) were treated earlier with systemic therapy including chemotherapy (n=5), MIBG (n=3) and somatostatin analogues (n=2).

Baseline characteristics are shown in Table 1; Seven patients had been previously reported.[11]

Twenty (67%) patients had radiological progressive disease (PD) at baseline. The remaining 10 patients had radiological stable disease and were treated for symptom control.

Table 1: Baseline characteristics

	All	**PS-PLG**	**S-PLG**	**PCC**
N.	30	17	10	3
Female, ***n (%)***	20 (66.7)	14 (82.4)	4 (40.0)	2 (66.7)
Age (med, range)	47 (29-74)	44 (29-74)	49 (30-74)	47 (38-63)
Localisation, ***n (%)***				
Solitary	4 (13.3)	2 (11.7)	2 (20.0)	0
Multiple	9 (30.0)	9 (52.3)	0	0
Metastatic	17 (56.7)	6 (35.2)	8 (80.0)	3 (100)
Lymph nodes	10 (33.3)	5 (29.4)	3 (30.0)	2 (66.7)
Liver	7 (23.3)	3 (17.6)	3 (30.0)	1 (33.3)
Lungs	6 (20.0)	3 (17.6)	0	3 (100)
Bones	13 (43.3)	3 (17.6)	9 (90.0)	1 (33.3)

Table 1: Baseline characteristics (continued)

	All	PS-PLG	S-PLG	PCC
Genetics, *n (%)*				
SDHB	5 (16.7)	0	5 (50.0)	0
SDHD	11 (36.7)	11 (64.7)	0	0
'Familial'	2 (6.7)	1 (5.9)	0	1 (33.3)
Sporadic (No SDHx)	5 (16.7)	1 (5.9)	4 (40.0)	0
Unknown	7 (23.3)	4 (23.5)	1 (10.0)	2 (66.7)
(Nor)metanephrine, *n (%)*				
Elevated	12 (40.0)	2 (11.7)	7 (70.0)	3 (100)
Normal	18 (60.0)	15 (88.2)	3 (30.0)	0
Baseline disease status, *n (%)*				
Progressive disease	20 (66.7)	10 (58.8)	7 (70.0)	3 (100)
Stable disease	7 (23.3)	5 (29.4)	2 (20.0)	0
Unknown	3 (10.0)	2 (11.7)	1 (10.0)	0
Previous Treatments, *n (%)*				
Surgery	19 (63.3)	9 (52.3)	7 (70.0)	3 (100)
Radiotherapy	6 (20.0)	3 (17.6)	2 (20.0)	1 (33.3)
Chemotherapy	5 (16.7)	1 (5.9)	3 (30.0)	1 (33.3)
Somatostatin analogue	2 (6.7)	0	1 (10.0)	1 (33.3)
^{131}I-MIBG	3 (10.0)	0	3 (30.0)	0
Nr. previous treatments, *n (%)*				
0	10 (33.3)	8 (47.1)	2 (20.0)	0
1	10 (33.3)	6 (35.2)	3 (30.0)	1 (33.3)
2	5 (16.7)	2 (11.7)	2 (20.0)	1 (33.3)
3	5 (16.7)	1 (5.9)	3 (30.0)	1 (33.3)
Uptake on ^{111}In-DPTA-octreotide scan (range 1-4), *n (%)*				
grade 2	11 (36.7)	7 (41.2)	4 (40.0)	0
grade 3	13 (43.3)	6 (35.2)	5 (50.0)	2 (66.7)
grade 4	6 (20.0)	4 (23.5)	1 (10.0)	1 (33.3)
Cumulative dose (GBq), *n (%)*				
14.8	2 (6.7)	1 (5.9)	1 (10.0)	0
22.2	6 (20.0)	2 (11.7)	3 (30.0)	1 (33.3)
25.9	2 (6.7)	2 (11.7)	0	0
29.6	20 (66.7)	14 (82.4)	6 (60.0)	2 (66.7)

PS-PLG – parasympathetic paraganglioma; S-PLG – sympathetic paraganglioma; PCC – pheochromocytoma;

Treatment administration

Twenty-two patients received 4 cycles of 7.4 GBq ^{177}Lu-DOTATATE. Due to recurring thrombocytopaenia, PRRT with ^{177}Lu-DOTATATE was limited to 3 cycles in 2 patients and to 2 cycles in one patient. Furthermore, treatment was limited because of disease progression in 3 patients and because of previous treatment with ^{131}I-MIBG (5.6 GBq) in one patient. One patient received 2 cycles of PRRT, after which response evaluation showed stable disease and elective embolization of the primary tumours was performed.

Safety and toxicity

A total of 110 therapies of ^{177}Lu-DOTATATE were administered. Acute toxicity in the form of nausea, vomiting and abdominal pain was generally mild and well controlled with anti-emetic and analgesic medication (Table 2). Nausea occurred after 37 (34%), vomiting after 14 (13%), and mild abdominal pain after 25 (23%) of the administrations. Grade 3/4 subacute haematotoxicity was observed in 6 (20%) patients (Table 2). One patient developed myelodysplastic syndrome after 6 cycles of ^{177}Lu-DOTATATE (including retreatment, cumulative dose 44.4 GBq), diagnosed 45 months after the first administration. The patient was not previously treated with chemotherapy or ^{131}I-MIBG and did not have bone marrow infiltration of the PGL.

Table 2: Toxicity (n (%))

Acute Toxicity (per treatment)	
Nausea	37 (33.6)
Vomiting	14 (12.7)
Pain	25 (22.7)
Subacute Toxicity (per patient)	
Anaemia	
grade 3	2 (6.7)
grade 4	0 (0.0)
Trombopaenia	
grade 3	4 (13.3)
grade 4	1 (3.3)
Leukopaenia	
grade 3	3 (10)
grade 4	0 (0.0)
Catecholamine crisis	2 (6.7)
Late toxicity	
Myelodysplastic syndrome (grade 5)	1 (3.3)

Elevated plasma and/or urinary normetanephrines were found in 2 (12%) patients with parasympathetic and 10 (77%) patients with sympathetic PGLs. A possible adverse event due to post-therapy catecholamine release occurred in 2 patients after their first cycle. The first patient had a sporadic metastatic carotid body PGL with lung and bone metastases. The 24h urinary excretion of normetanephrines at baseline was two times elevated with normal metanephrine excretion. This patient was not pre-treated with alpha-adrenergic receptor blockers. After the first PRRT cycle, patient had symptoms of increased flushing and sweating and developed cardiac failure. A diminished ejection fraction was measured with echocardiography, possibly caused by chronic catecholamine release. Administration of diuretics and octreotide resulted in a full clinical recovery. The second patient was treated for a sporadic metastatic PCC with alpha- and beta-adrenergic receptor blockade. The 24h urinary excretion of normetanephrines was approximately 25 times the upper limit of normal with normal metanephrine excretion. This patient developed pleural effusion and a

delirium after the first cycle, possibly caused by heart failure or catecholamine release which was successfully treated with haloperidol and standard supportive care. After discharge a echocardiography reported normal ejection fraction. In both patients, further cycles were uneventful with pre-cycle preventive pre-treatment. There were no incidences of hypertensive crises or clinical deterioration of local nerve compression after PRRT.

Efficacy

In all 30 patients, the best response according to RECIST 1.1 was partial response (PR) in 7 patients (23%) and stable disease (SD) in 20 patients (67%), whereas 3 patients (10%) had progressive disease (PD). In 20 patients with baseline radiological PD, disease control (PR + SD) was observed in 17 patients (85%). In patients with a localized PGL the disease control rate was 100% and in patients with a metastatic GL or PCC treatment with PRRT resulted in disease control in 79% of patients. Response stratified for baseline PD is shown in Figure 1.

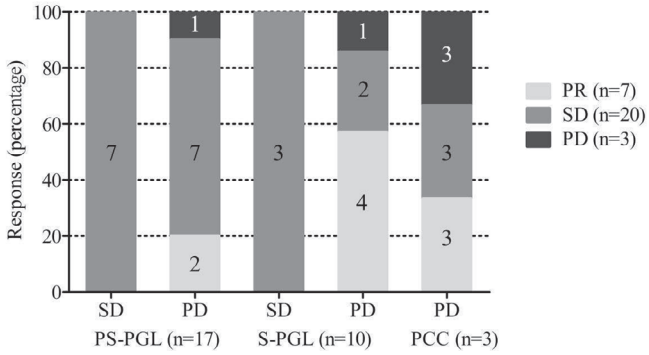

Figure 1: Treatment outcome stratified for tumour type and baseline disease status. PS-PGL – parasympathetic paragangliomas; S-PGL – sympathetic paragangliomas; PCC – pheochromocytomas; PR – partial response; SD – stable disease; PD – progressive disease.

Survival was assessed in 20 patients with PD at baseline (Table 3). In these patients, the median follow-up was 52.5 months (range 7-155). During follow-up, 14 patients had a registered primary event (PD in 7 patients and start of a new treatment in 7 patients) and 9 patients had died. In the 10 patients with parasympathetic PGLs, the median progression-free survival (PFS) was 91 months. In the 7 patients with sympathetic PGLs this was 13 months. The PFS in the 3 patients with PCCs was respectively 8, 10 and 14 months. The median overall survival (OS) was not reached in the parasympathetic PGL patients and this was 59 months in the sympathetic PGLs patients. OS in the 3 patients with PCC was respectively 9, 17 and 21 months. Figure 2 and 3 show the Kaplan-Meier curves for PFS and OS in these patients. In patients with a localized PGL the median PFS was not reached while patients with a metastatic (N1 and/or M1) PGL or PCC had a median PFS of 13 months after treatment with PRRT.

Table 3: Treatment outcomes

		Type			TNM Stage	
	All (n=30)	**PS-PGL (n=17)**	**S-PGL (n=10)**	**PCC (n=3)**	**Localized† (n=13)**	**Metastatic† (n=17)**
Best Response*: n(%)*						
- Partial response	7 (23.3)	2 (11.8)	4 (40.0)	1 (33.3)	1 (76.9)	6 (35.3)
- Stable disease	20 (66.7)	14 (82.3)	5 (50.0)	1 (33.3)	12 (23.1)	8 (47.1)
- Progressive disease	3 (10.0)	1 (5.9)	1 (10.0)	1 (33.3)	0	3 (17.6)
Disease Control Rate*	17 (85.0)	9 (90.0)	6 (85.7)	2 (66.7)	6 (100)	11 (78.6)
Survival*	**n=20**	**n=10**	**n=7**	**n=3**	**n=6**	**n=14**
Median follow up	52.5	76	42.5	17	87	44
Primary events	14	4	7	3	1	13
Median PFS (months)	30	91	18	10	n.r.	13
Deaths	9	2	4	3	0	9
Median OS (months)	n.r.	n.r.	59	17	n.r.	23

* In patients with baseline disease progression.

† Localized TxN0M0, Metastatic: N1 and/or M1

PS-PLG – parasympathetic paraganglioma; S-PLG – sympathetic paraganglioma;
PCC – pheochromocytoma; PFS – progression free survival;
OS – overall survival; n.r. – not reached;

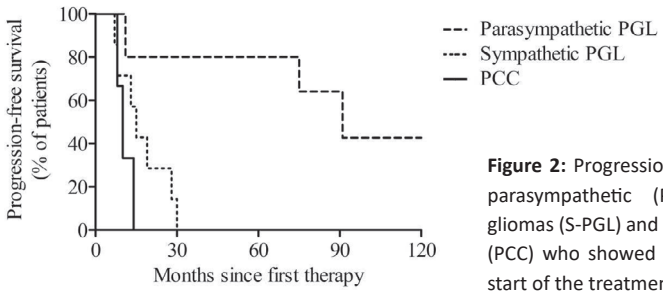

Figure 2: Progression free survival in patients with parasympathetic (PS-PGL)/sympathetic paragangliomas (S-PGL) and malignant phaechromocytomas (PCC) who showed progressive disease before the start of the treatment.

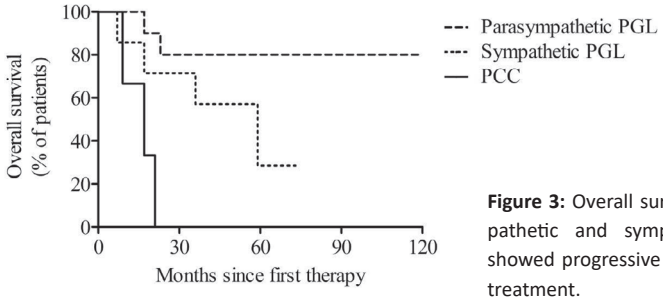

Figure 3: Overall survival in patients with parasympathetic and sympathetic paragangliomas who showed progressive disease before the start of the treatment.

Clinical response and Quality of Life

In 10 patients, objective PD at baseline was not determined or could not be determined. The indication for treatment in 6 out of 7 patients with parasympathetic PGLs was (progressive) symptoms relating to local nerve compression, such as muscle weakness, hearing loss and tinnitus. These symptoms were ameliorated in 2 and remained stable in the other 4. Out of the 3 patients with sympathetic PGLs without PD at baseline, 2 had symptoms related to catecholamine hypersecretion. After treatment, symptoms and catecholamine levels were stable. The third patient was treated because of high tumour volume which did not respond to cisplatin/etoposide chemotherapy. After PRRT, SD was achieved and this was maintained for over 13 years.

Out of 12 patients with elevated catecholamine secretion, baseline and follow-up measurements were available in 6. In two patients, normalisation of urinary normetanephrine excretion was observed and in one a decrease in normetanephrine levels of more than 50% was observed. Three other patients showed no response and in one patient with a PCC urinary normetanephrine excretion increased from 53 times upper limit of normal (ULN) to 73x ULN.

European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionneaires-C30 version 3.0 were used to assess quality of life.[20] In 17 patients, baseline and at least one follow-up assessment (at 4-6 weeks or 3 months after the last treatment) were available. Using the paired sample t-test, there were no statistically significant differences between the pre- and posttreatment assessments in any of the 5 functional or 7 symptom scales or in global health status (data not shown).

DISCUSSION

This analysis of 30 patients treated with PRRT with ^{177}Lu-DOTATATE for inoperable or malignant PGLs or PCCs demonstrates encouraging results with induction of tumour stabilisation in the majority of patients including those with PD at baseline. PRRT is well tolerated in this patient group, even in patients with elevated catecholamine levels or local nerve compression. However, a subacute adverse event due to possible post-therapeutic catecholamine release occurred in 2 patients out of 12 (17%) with elevated normetanephrines. This catecholamine-related complication occurred after the first cycle, underscoring the need for accurate assessment, careful monitoring and (pre-)treatment of patients with hormonally active tumours, mainly before the first cycle.[21] An echocardiography can be considered in the pre-treatment evaluation to assess the risk of cardiac failure, given the high prevalence of myocardial dysfunction in this patient subset.[22] After an uneventful first therapy, no crises were observed after the following cycles with ^{177}Lu-DOTATATE.

In the patients with objective PD at baseline, disease control was observed in 85% of patients and the median PFS was 91 and 13 months in patients with parasympathetic and sympathetic PGLs, respectively. Limitations of our analysis are the heterogeneity of this relatively small patient cohort and the retrospective design of the study. Also, the absence of a control group limits the interpretation of progression-free survival. Furthermore, not all patients showed radiographic PD before treatment, as some patients were treated because of progressive symptoms or to decrease the risk of onset or progression of symptoms in inoperable tumours. In line with the radiological outcomes, the most frequent clinical outcome was stabilisation of symptoms.

For the treatment of metastatic PGLs there are no uniform guidelines. Surgery is the first line of treatment for benign PGLs and, even with distant metastases, surgery may improve survival and reduce symptoms.[23,24] If inoperable, systemic treatment options mainly include radionuclide therapy and cytotoxic chemotherapy; Table 4 also shows the response rates for these different treatment modalities. Traditionally, a chemotherapeutic regimen with cyclophosphamide, vincristine and dacarbazine is used.[25] More recently, treatments with temozolomide, sunitinib or interferon-alpha have been explored, but the evidence for the beneficial effects of these therapies is still very limited.[26-29] External radiotherapy can be used for the treatment of head and neck PGLs and of bone metastases.[30] Another radio-

Table 4: Therapeutic outcomes in case series on inoperable or metastatic paragangliomas or malignant pheochromocytomas

First Author	Year	n	Type	Treatment	Bsln PD (%)	CR (%)	PR (%)	SD* (%)	PD (%)	Criteria
Kong[17]	2017	14	mPGL, PCC	^{177}Lu-DOTATATE	30	0	29	57	14	RECIST 1.1
Pinato [33]	2016	5	mPGL	^{177}Lu-DOTATATE	100	0	20	60	20	n.a.
Puranik [34]	2015	9	i/m PSP, PGL	^{90}Y- or ^{90}Y/ 177Lu-DOTATATE	n.a.	0	0	100	0	RECIST 1.1
Forrer [35]	2008	28	i/mPGL, PCC	^{90}Y-octreotide or ^{177}Lu-DOTATATE	100	0	7	64	29	WHO
Imhof[36]	2011		mPGL, PCC	^{90}Y-octreotide	100	0	18	n.a.	n.a.	n.a.
Hadoux [26]	2014	11	mPGL, PCC	Temozolomide	100	0	36	55	9	RECIST 1.1
Ayala-R. [27]	2012	14	SP mPGL, PCC	Sunitinib	100	0	21	36	43	RECIST 1.1
Hadoux [28]	2017	14	mPGL, PCC	Interferon-alpha	86	0	21	64	14	RECIST 1.1/ PERCIST 1.0
Hulsteijn** [31]	2014	243	mPGL, PCC	^{131}I-MIBG	n.a.	3	27	52	18***	variable
Huang [39]	2008	18	mPGL, PCC	CVD	n.a.	11	44	44	0	variable
Tanabe [40]	2013	17	mPGL, PCC	CVD	n.a.	0	24	47	29	RECIST 1.1

Bsln PD - baseline progressive disease; CR - complete response; PR - partial response; SD - stable disease; PGL - paraganglioma; m - metastatic; i - inoperable; PSP – parasympathetic; SP - sympathatic; PCC – pheochromocytoma: n.a. - not available; CVD - cyclophosphamide, vincristine, dacarbazine; RECIST - response evaluation criteria in solid tumours; WHO - World Health Organization. * Including all reported cases with minimal/minor response. ** Meta-analysis. *** Calculated by author.

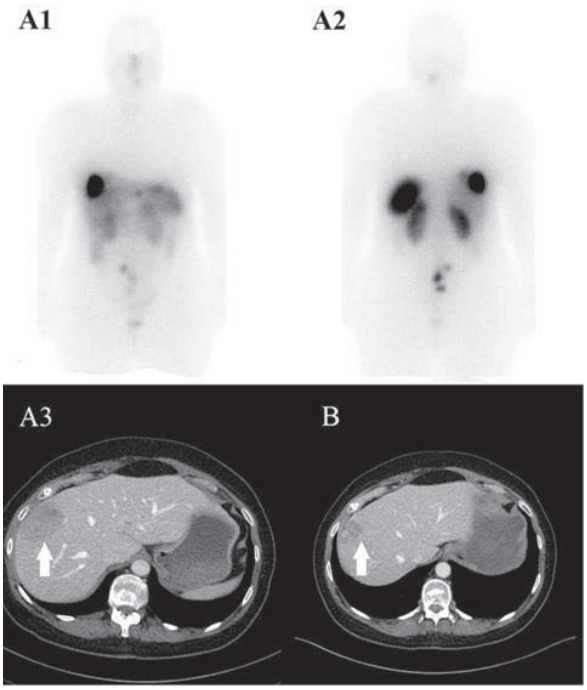

Figure 4: Response of liver metastasis in a patient with a metastatic sympathetic paraganglioma
A1/2: Planar anterior and posterior total body scintigraphs after the first cycle with ^{177}Lu-DOTATATE
A3: CT-scan of liver before first cycle
B: CT-scan of liver six months after last cycle. Note the shrinkage of the liver metastasis in segment 8

nuclide therapy than PRRT is performed using ^{131}I-MIBG and was used in 3 of our patients prior to PRRT. Recent, meta-analysis showed objective response in at least 30% of patients.[31] However, it must be noted that not all PGL subtypes show sufficient MIBG uptake and thus, as with PRRT, reported results are from a selected population.[6] In the most recent ESMO guidelines on the treatment of adrenal malignancies PRRT with ^{177}Lu-DOTATATE was not included.[32] There is however, growing evidence in the literature for the efficacy and safety of PRRT with radiolabelled SSAs for the treatment of inoperable or metastatic PGLs or malignant PCCs. An overview is provided in Table 4. In 4 case series, the results of PRRT were retrospectively analysed, showing disease control rates of 71-80% in patients with baseline PD.[17,33-35] In addition to these case series, Imhof et al. reported on PRRT in 11 patients with PCCs and 28 patients with PGLs, which showed morphological response in 36% and 11% of patients, respectively.[36] Our current study reports the highest response rate in patients with radiological progression and mainly in patients with sympathetic PGL or PCC. Therefore these patients seem the best candidate for treatment with ^{177}Lu-DOTATATE. In patients treated for indications other than progressive disease, no radiological partial response was noted. Specifically in patients with parasympathetic PGL treated for local nerve compression

no radiological response was noted. However, PRRT resulted in a symptomatic response of 33% and PRRT with ^{177}Lu-DOTATATE can therefore still be considered for these patients if localized therapy like surgery is not feasible. Haematotoxicity does however seem to be higher than for patients treated for gastroentreopacreatic NETs. Sub-acute heamatotoxicity occurred in 20% of patients similar to the incidence reported by *Kong et al.*[17] Whether this adverse effect is caused by previous treatment regimens, a higher incidence of bone metastases or other causes remains unclear

CONCLUSION

In light of limited treatment options, this study supports the practice of screening every patient with inoperable or metastatic PGL and PCC with SSA-labelled functional imaging to assess the possibility of off-label usage of PRRT with ^{177}Lu-DOTATATE.[37,38]. To determine the optimal sequence of PRRT and other treatments available for these patients randomised trials would be required but this is hampered by the low incidence of these disorders. Our analysis shows that PRRT using ^{177}Lu-DOTATATE can be a safe and an effective therapeutic option.

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