^{111}In-Octreotide Infusions for the Treatment of Paraganglioma

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16.1 Introduction

Paragangliomas are rare, non-epithelial NETs [1], which derive from paraganglial system, and are classified as (a) sympathetic, almost always producing catecholamines, and (b) parasympathetic, usually not releasing catecholamines [2].

They are metastatic in about 10% of cases. Paragangliomas are known to express high levels of somatostatin receptors (sst), especially subtype sst2. However, according to Saveanu et al. [3], Reubi et al. [4], and Binderup et al. [5], some paragangliomas have cytoplasmic localization of sst2 receptor rather than a membrane, and it has been suggested that this might account for not only the failure of sst2 agonists in controlling catecholamine secretion and tumor proliferation but also failure of ^{111}In-Octreotide imaging to detect some of them. ^{111}In-Octreotide shows a modest sst2 binding, having a good sensitivity (up to 90%) for head and neck paragangliomas [6] and according to Charrier et al. [7] a mediocre sensitivity as low as 20% as far as the abdominal ones. Nowadays, for their diagnosis, a new generation of somatostatin analogs with superior sst2 binding affinity has been developed for use with PET/CT imaging such as ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC, and ^{68}Ga-DOTATATE [8, 9] (Table 16.1).

According to WHO, paragangliomas are classified into two groups, based on their clinical and biological behavior: those arising from the parasympathetic system, primary located in the head and neck and less frequently in the thorax and pelvis, and those from the sympathetic one (Table 16.2).

16.1.1 Parasympathetic (Head and Neck) Paragangliomas

Accounting approximately a 20% of all paragangliomas [10–12] are generally nonfunctioning subcategorized according to their anatomical sites of origin as carotid body paragangliomas, jugulotympanic paragangliomas (Fig. 16.1), vagal paragangliomas, and laryngeal paragangliomas [13]. As a whole, less than 5% of head and neck paragangliomas metastasize. Hereditary cases of head and neck paragangliomas could be multiple and

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Table 16.1 Affinity profiles (IC50) of somatostatin receptor subtypes for imaging and therapy

Sst and its analogs	sst1	sst2	sst3	sst4	sst5
Somatostatin-28	5.2	2.7	7.7	5.6	4.0
[111]In-Octreotide	>10,000	22	182	>1000	237
68Ga-DOTATOC	>10,000	2.5	613	>1000	73
68Ga-DOTANOC	>10,000	1.9	40	260	7.2
68Ga-DOTATATE	>10,000	0.2	>1000	300	377

IC50 is expressed in nanomoles (the lower the values, the higher the receptor affinity)

Table 16.2 WHO classification for paragangliomas

	Sympathetic	Parasympathetic
Location/ frequency	Below the diaphragm/85%	Head-neck/20%
Function	+++	+
Norepinephrine levels	+++	+
Dopamine levels	+++	+
Metastatic tension	High risk	Seldom (<5%)

Fig. 16.1 OctreoScan® scintigraphy (right lateral view) of a petrous-bone paraganglioma, after 185 MBq ^{111}In-Octreotide, i.v. 7 h post injection (visual score II to III)

occur in association with sympathetic ones. The germline mutation, most commonly noted in one of the succinate dehydrogenase genes (SDHx), can be screened by immunohistochemical staining for SDHB protein. Paragangliomas associated with SDHB mutations have a high risk of metastasis. Thus, even in the absence of family history, genetic testing should be recommended for at least the most common genes in all patients, depending on local resources [14].

16.1.2 Sympathetic Paragangliomas

Approximately 85% of sympathetic paragangliomas arise below the diaphragm. Sympathetic paraganglioma could be found in retroperitoneum around the adrenal/renal area, around the organ of Zuckerkandl or in the urinary bladder [15]. The other sympathetic paragangliomas are noted in the thorax, heart, and other locations [16–18]. Sympathetic paragangliomas are more likely to be functioning when compared to head and neck paragangliomas [19]. Patients with sympathetic paragangliomas usually have elevated norepinephrine only or both norepinephrine and dopamine. Sympathetic paragangliomas have high risk of metastases and even higher (even up to 50%) in those with SDHB mutation [20].

16.1.3 Treatment Stratification

Although most paragangliomas are benign, factors such as genetic background, tumor size, tumor location, and high methoxy-tyramine levels are associated with higher rate of metastatic disease. Their proximity to cranial nerves and vasculature may result in considerable morbidity due to compression or infiltration of the adjacent structures, necessitating balanced decisions between a wait-and-see policy and active treatment [21]. Surgery is the only curative treatment. Treatment options for patients with metastatic disease are limited. Paragangliomas have a strong genetic background, with at least one-third of all cases linked with germline mutations in 11 susceptibility genes. As genetic testing becomes more widely available, the diagnosis assessment of paragangliomas will be made earlier due to
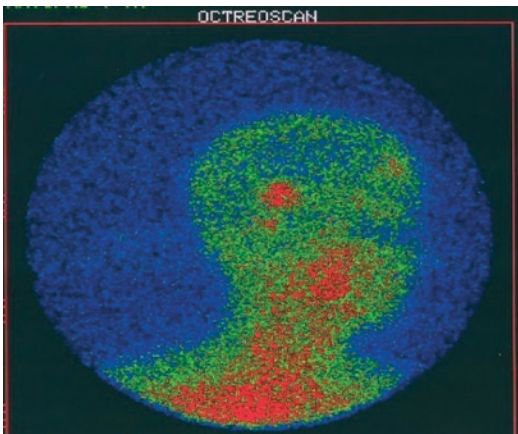
Table 16.3 Multidisciplinary team approach for the paraganglioma patient's management

Nuclear medicine physician	Hepatic surgeon
Interventional radiologist	Medical oncologist
Radiation physicist	Pathologist
Colorectal surgeon	Anesthesiologist
Gastroenterologist	Dedicated nursing staff

routine screening of at-risk patients. As a result, a multidisciplinary approach for the management of paragangliomas is required to ensure a consistent and optimal level of care and treatment (Table 16.3).

For both sympathetic and parasympathetic PGLs, surgery is the treatment of choice, in cases where it can be performed. Further options of therapeutic schemes include systematic treatment with agents as gemcitabine, cisplatin or sunitinib, and radiotherapy (external-beam radiotherapy or stereotactic surgery). However, surgery and radiotherapy can cause severe side effects: the former hemostatic complications and nerve damage, particularly when tumor is in tight proximity with cranial nerves, and the latter vascular complications and peripheral nerve damage as well. In the international library, limited clinical data are available focused on radiopeptide schemes as treating option to confront paragangliomas. By the present, we describe and discuss the challenges of treating these rare tumors with ¹¹¹In-octreotide in high doses, using established protocols, performed in our institution for other NET histotypes.

We report on the effectiveness of PRRT in three paraganglioma patients [one with surgically excised primary in the lower part of the sigmoid colon associated with liver metastases and two inoperable cases (one at the petrous portion of the right temporal bone of the skull and the second situated in the lower half of the mediastinum)], verified by Octreo-Scan® (Figs. 16.1 and 16.2) and biochemically and radiologically confirmed. The dose per session administered monthly to each patient ranged from 4.070 to 5.920 GBq. Repetitions for the inoperable cases did not exceed the nine sessions and for liver secondaries the twelve, with treatment intervals of 5–8 weeks.

Fig. 16.2 OctreoScan® scintigraphy (anterior view) of an inoperable paraganglioma of the lower half of mediastinum, after 185 MBq ¹¹¹In-Octreotide, i.v. 7 h-post injection (visual score II to III)

Patients with inoperable PGLs were infused intravenously, after centesis of the dorsal vein hand system or the antecubital vein, whereas for the liver secondaries, ¹¹¹In-Octreotide was infused intra-arterially, after catheterization of the hepatic artery. Absorbed doses delivered to the primaries, to the liver metastases, kidneys, and red marrow were calculated according to OLINDA/EXM program, and response assessment was classified, based on RECIST criteria 1.1. CT/MRI scans were performed before, during, and after the end of treatment and monthly ultrasound images for the follow-up of the liver lesions.

16.2 ¹¹¹In-Octreotide Treatment Results

Liver metastatic load: None of the three treated patients resulted in complete response; partial response was assessed in one, whereas disease stabilization in two. *Petrous bone and mesothorax primary neoplasms load:* The aforementioned two cases resulted in initially disease stabilization for a short term, whereas on the

Table 16.4 Patients response to therapy with ^{111}In-octreotide

Patient's no./infusion way	Tumor origin	Response evolution	PFS	OS
1. Intravenously	Inoperable, mediastinum	SD ≫ PD ≫ D	25	29
2. Intravenously	Inoperable, petrous bone	SD ≫ PD ≫ D	19	26
3. Intra-arterially	Surgically excised, sigmoid	PR	108	120

PD partial response, *SD* stable disease, *PD* progressive disease, *D* death, ≫ shifted to
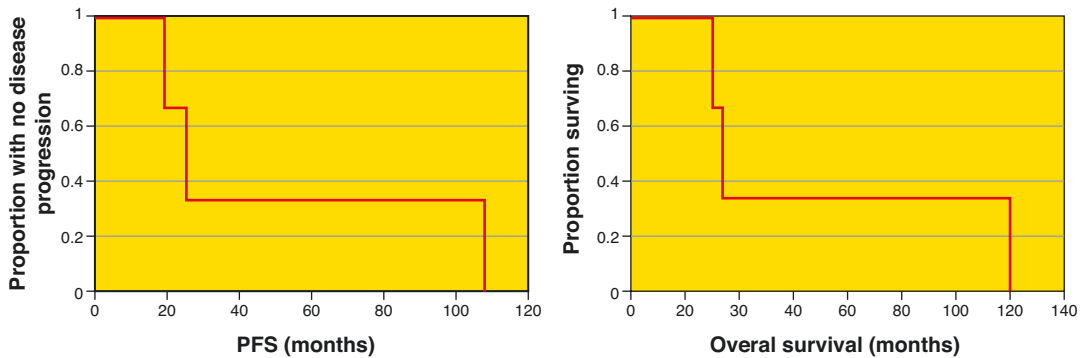
Fig. 16.3 Kaplan-Meier curves for PFS and OS of the three paraganglioma patients' study, treated with ^{111}In-Octreotide

progress of the therapy, they did not respond at all and died within 26–29 months after the initialization of the therapy due to aggravation and complications of the tumors (Table 16.4). According to the therapy response results, the 24-month PFS ratio was found to be 2/3 (66.6%) while the 24-month OS was 3/3 (100%) (Fig. 16.3). On CT, the mesothorax and petrous bone tumor masses progressed dramatically, whereas the liver metastases showed a mean target diameter shrinkage ranging from 33 to 45%. Grade I to II erythro-, leuko-, and thrombocytopenia occurred in all three cases. Dosimetric calculations for both the intra-arterial and intravenous infusions are tabulated in Table 16.5. Remarkably, an over than threefold higher tumor absorbed dose in favor of the intra-arterial one was noticed.

16.3   Discussion

This single-center analysis provides results including the respective progression-free survival and overall survival rates of PRRT in three patients with advanced paragangliomas of different primary origins after failing standard treatment. Despite the tiny patient number ($n = 3$), the treatment results forward the feature of the persistent anti-proliferative activity of ^{111}In-Octreotide Auger and internal conversion electron emission in this specific NET rare entity at an advanced stage. However, this sort of electron emission achieves a rather insignificant disease control in the case of inoperable mediastinum and petrous paraganglioma patients, intravenously treated, a short-term stabilization, and a median progression-free survival (PFS) of 19–25 months, thus rendering ^{111}In-Octrerotide not promising for an objective outcome in that context of lacking established treatment alternatives. On the contrary, concerning the intra-arterially treated hepatic metastases originating from the surgically excised colorectal paraganglioma, a long-term partial response was achieved with a PFS of 108 months.

According to the worldwide ergography, few studies report on the effect of PRRT in the management of patients suffering from metastatic or unresectable paragangliomas and no one on the

Table 16.5 Tumor-absorbed dose comparison between i.v. and i.a. administration of 111In-Octreotide

Organs	Intra-arterial infusion	Intravenous infusion
Liver dose	0.14 (mGy/MBq)	0.40 (mGy/MBq)
Kidney dose	0.41 (mGy/MBq)	0.51 (mGy/MBq)
Tumor dose	15.20 (mGy/MBq)	11.20 (mGy/MBq)
Spleen dose	1.40 (mGy/MBq)	1.56 (mGy/MBq)
Bone marrow dose	0.0035 (mGy/MBq)	0.022 (mGy/MBq)
Tumor/liver dose ratio	108.57[a]	28.00
Tumor/kidney dose ratio	37.07	21.96

[a]The average absorbed dose per session to a tumor for a spherical mass of 10 g was estimated to be 10.8 mGy/MBq, depending on the histotype of the tumor

response and efficacy of Auger and internal conversion indium's electron emission. As in the majority of NETs, surgery consists the treatment of choice to confront this rare neuroendocrine histotype; however, even after radical operation, patients lurk the risk of recurrence and the development of metastases, even after many years. Fortunately, the low toxicity of the neoplasm and the usually settled long-term follow-up create good conditions for an efficient disease control. However, the real challenge for clinicians is the treatment of inoperable or metastatic tumors. Furthermore, the functioning cases, the elevated risk for severe cardiovascular disease, and the risk of malignancy add additional doctors' dilemmas [22–27].

We studied the PRRT results after 111In-Octreotide administration in three patients suffering from paragangliomas. Comparing the internal references of several experteer reports on PRRT (Table 16.6), not with 111In-octreotide (an Auger and internal conversion emitter) but with 90Y-DOTATATE/DOTATOC or 177Lu-DOTATATE (β-emitters), an objective response was observed in one of three (33.3%) patients of the treated cases, with a median PFS of 25 and median OS of 29 months. The outcome of this three-patient cohort gives a disease stabilization in two patients

and a partial response in one. In 2006, in a 177Lu-DOTATATE study by van Essen et al. [28], including 12 PGL patients during a median of 13 (range 4–30) months follow-up, an ORR of 16.7% and a SD of 58.3% were reported. PD was 25%, whereas PFS and OS were not tabulated. In a 90Y DOTATOC study by Imhof et al. [29], in a cohort of 28 paragangliomas, a median OS of 82 months was reported; ORR and PFS were not clearly discriminated. The same year, Zovato et al. [30] achieved in a cohort of four paragangliomas, treated with 177Lu DOTATATE, a median PFS in a range of 15–25 months with a 50% ORR; median OS was not referred. Cecchin et al. [31] in a paraganglioma case study reported a PR (100%) with a median PFS of 16 months; median OS was not referred. Pinato et al. [32], in a study of five paraganglioma-treated cases implementing 177Lu DOTATATE, reported a median PFS and a mean OS of 17 and 53 months, respectively; median OS was not achieved. In a paraganglioma case study of Ashwathanarayana et al., in 2017 [33], a 100% objective response was observed with a mean PFS of about 5 months and a mean OS of 11 months. In a study of Kong et al. [34], 20 patients with paragangliomas, treated with 177Lu-DOTATATE, reached a median PFS of 39 months, whereas the median OS was not reached. The authors reported a PR in 19 (70%) patients and a SD in 7 (26%). In a study by Nastos et al. [35] in 15 paraganglioma cases treated with 131I-mIBG as well as with 177Lu DOTATATE, the median PFS was 20.6 and 38.5 months, respectively. The authors achieved a median OS of 41.8 months for 131I-mIBG and 60.8 months for 177Lu DOTATATE; ORR was not clearly discriminated and tabulated. In a recent prospective study of Garske-Román et al. [36] on 11 rectal NETs, median PFS and OS were 34 (17–35) and 50 months, respectively, in 8 out of 11 patients, in whom the absorbed dose to the kidneys reached 23 Gy; in the rest three, in whom it did not, PFS and OS were 12 (3–12) and 12 (11–33) months accordingly. Yavad et al. [37] evaluated in a recent study the role of combined capecitabine and 177Lu-DOTATATE in malignant PGL patients. He observed in a cohort of 25 cases a 28% objective response with a median PFS of

Table 16.6 Experts on PRRT paraganglioma treatment

Author	Year	Radiopeptide	n	orr (%)	Median PFS (months)	Median OS (months)
van Essen et al.	2006	^{177}Lu-DOTATATE	12	16.7	nr	nr
Imhof et al.	2011	[90]Y DOTATOC	28	a	a	82
Zovato et al.	2011	^{177}Lu-DOTATATE	4	50	>15.8–25	nr
Cecchin et al.	2011	^{177}Lu-DOTATATE	1	100	16	nr
Pinato et al.	2016	^{177}Lu-DOTATATE	5	20	17	nr
Ashwathanarayana et al.	2017	^{177}Lu-DOTATATE	1	100	~5	11
Kong et al.	2017	^{177}Lu-DOTATATE	20	a	30	nr
Nastos et al.	2017	[131]I MIBG ^{90}Y/^{177}Lu-DOTATATE	15	a	20.6 38.5	41.2 60.8
Garske-Román et al.	2018	^{177}Lu-DOTATATE	3	0	14	37
Yadav et al.	2019	^{177}Lu-DOTATATE	25	28	32	nr
Vyakaranam et al.	2019	^{177}Lu-DOTATATE	13	7.7	16.7	37.3
Kolasinska-Cwikła et al.	2019	^{90}Y-DOTATATE	13	8	35	68
Limouris et al.	This study	^{111}In-Octreotide	3	100	25	29

rs retrospective study, *ps* prospective study, *orr* objective response rate, *PFS* progression-free survival, *os* overall survival, *nr* non-referred

[a] not clearly reported nor discriminated and tabulated

32 months; median OS was not referred. Vyakaranam et al. [38] in a recent study in 13 paraganglioma patients, treated with ^{177}Lu-DOTATATE, reported a PR in 1 out of 13 (7.7%) patients, a median OS of 37.3 months, and a median PFS of 21.6 months.

Finally, in a prospective open-label, single-center, phase II study of 13 patients with unresectable advanced paraganglioma treated with ^{90}Y DOTATATE by Kolasinska-Cwikła et al. [39], a median PFS of 35 and a median OS of 68 months were observed.

In our three patients' cohort, the equivocal and almost expected disappointing response to ^{111}In-Octreotide intravenous infusions in PGL primaries was also predicted and expected during each PRRT cycle by scintigraphy, including both whole-body scans and SPECT/CT. Furthermore, the visual rating (score) of the tumor radiotracer uptake ranges between II and III, never reaching the visual score IV of the hepatic secondaries.

16.4   Conclusion

In unresectable metastatic liver lesions positive for somatostatin receptors, originated from PGLs, repeated, intra-arterial high doses of ^{111}In-Octreotide resulted in a partial response in all the affected liver lesions. As far as both primaries, i.e., that of the inoperable petrous bone and the other of the mesothorax, after a short-term disease stabilization, progressed dramatically. The dosimetric calculations proved the poor absorbed dose, predicting the disappointing results. Systematic PRRT in primary PGLs with intravenously injected ^{111}In-Octreotide does not seem to have clinical effects in PGLs due to the over 20 mm tumor size and has no meaning to perform. On the contrary, liver secondaries not exceeding the 20 mm in diameter, intra-arterially treated, show the same successful results observed in GEP-NET histotype (Chap. 7).

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