Personalized Thera(g)nostic Approach in Patients with Paraganglioma: Peptide Receptor Radionuclide Therapy

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Abstract

Objective: The experience with Somatostatin-Receptor (SSTR) based Peptide-Radionuclide Therapy (PRRT) in patients with Paraganglioma (PGL) is limited. We report our experience for the treatment of malignant PGL.

Material and Methods: Nineteen patients with PGL, who were treated with ⁹⁰Y-DOTATOC/₁⁷⁷Lu-DOTATATE, were retrospectively reviewed. Response to treatment was evaluated by RECIST 1.0/PERCIST 1.1 criteria.

Results: Of the 19 patients, 6 were male and 13 females, ages ranged from 18 to 74 years at initial diagnosis. Pre-therapeutic scanning was positive in 19/19 PGL-patients with ⁶⁸Ga-DOTATOC from whom 13/19 patients received ⁹⁰Y-DOTATOC (ACA (accumulated activity) range 8.07-16.44 GBq, ATD (accumulated tumour dose) range 4.6 Gy to 152.8 Gy), 4/19 patients ⁱ⁷⁷Lu-DOTATATE (ACA range 8.49 GBq to 55.42 GBq, ATD range 14.1 Gy to 235.3 Gy). In two patients no therapy could be applied. The median PFS and OS was 96 (range 10 to 180) and 99.5 (range 24 to 180) months, respectively.

Conclusion: Both ⁹⁰Y/¹⁷⁷Lu-SSTR-targeting peptides may be useful for long-term disease control in patients with locally advanced or metastatic paraganglioma when applied in several treatment cycles that may reach meaningful absorbed tumour doses. Pretherapeutic scanning for a tailored treatment regimen seems appropriate in order to identify the radiopharmaceutical with highest tumour uptake.

Keywords: Paraganglioma; ¹³¹I-mIBG; Somatostatin; PRRT

Introduction

Paragangliomas (PGL) belong to the group of Neuroendocrine Tumors (NETs) that arise from extra-adrenal paraganglia as part of the autonomic nervous system. These rare neuroendocrine neoplasms may develop at various body sites and in most cases; they behave benign and are asymptomatic. Depending on the primary location these tumors may show a different behavior. For example, abdominal and thoracic PGL may produce catecholamines and related substances as they derive from sympathetic paraganglia. On the other hand, parasympathetic paraganglia are primarily located in the skull base and neck, so these PGL usually do not produce such substances, depending on the underlying somatic or germine mutation [1]. Generally these tumors are rare and show the highest prevalence in the fourth and fifth decades. For benign PGL the choice of therapy is surgery. The term “malignant” PGL has been recently replaced by “metastatic” PGL by the WHO classification 2017 [2]. Primary tumor resection, if possible, can be recommended based on evaluation of local tumor burden and especially extent of metastases formation. Also, radiotherapy or radiosurgery may result in local tumor control [3]. An additional approach is Peptide Receptor Radiotherapy (PRRT) in case the tumors show somatostatin-receptor-expression [4]. Still choice of treatment is recommended as a multidisciplinary team approach and often discussed controversially [5].

For paraganglioma a variety of imaging techniques can be used with all their pros and cons. Whereas CT and MRI provide high sensitivity, the specificity is lower as radiologic imaging cannot distinguish between tumors derived from the sympathetic nervous system from other tumor entities. In contrast, ¹²³I-meta-Iodo-Benzyl-Guanidine (¹²³I-mIBG) SPECT is an imaging technique with moderate sensitivity but high specificity and is useful to select inoperable or metastasized patients...
for treatment with $^{123}$I-mIBG [6]. $^{18}$F-DOPA has high sensitivity and specificity for detecting non-metastatic extraaortal PGL but less sensitivity for metastatic disease [7,8]. There is evolving evidence that the Somatostatin Receptor (SSTR) -binding $^{68}$Ga-labelled peptides such as $1,4,7,10$-tetraazacyclododecane-$N,N',N''$-$N'''$-tetraacetic acid-D-Phe1-Tyr3-octreotide (DOTA-TOC) are superior for imaging non-malignant and metastatic PGL compared to $^{18}$F-DOPA and $^{123}$I-mIBG, especially for bone lesions [9-12]. As functional imaging aims at certain metabolic properties of these tumors, we are able to provide therapy by replacing the diagnostic tracer by a therapeutically one which has a high interaction of energy with material.

In patients with metastasized or inoperable PGL the "old" thera(g) nostic concept of $^{123}$I-mIBG imaging/$^{123}$I-mIBG therapy [13] and the "newer" thera(g)nostic concept of $^{68}$Ga-DOTA-SSTR imaging/$^{177}$Lu-$^{7}$Y-SSTR-targeted Peptide Receptor Radioligand Therapy (PRRT) have indicated therapeutic potential in this group of rare patients who have only limited therapy options [4,14]. Unless to other types of NETs with established results for PRRT [15], this therapy option has not been officially accepted by neither the U.S. Food and Drug Administration (FDA) nor European Medicines Agency (EMA) due to small patient cohorts.

Here we retrospectively report on our cohort of 19 patients with paraganglioma treated by either $^{177}$Lu- or $^{90}$Y-PRRT selected by pre-therapeutic imaging with $^{68}$Ga-DOTA-TOC PET/CT.

**Material and Methods**

**Patients**

Our cohort involves 19 patients (13 female, 6 male) with histologically proven inoperable and/or metastasized PGL of various origin (Table 1, 2). These patients were referred to our institution for staging or restaging over the years 1992 to 2012. The age at initial diagnosis ranged from 18 to 74 years and 9 patients were still alive in 12/2019.

**Imaging studies**

$^{123}$I-mIBG and/or $^{68}$Ga-DOTA-TOC imaging both were performed to evaluate patients’ eligibility for either $^{123}$I-mIBG therapy or PRRT, respectively, and in order to fully delineate the extent of the tumor, $^{123}$I-mIBG Planar and SPECT/CT Imaging was performed according to the procedure guidelines of the EANM [16]. The radiation exposure related to $^{123}$I-mIBG was 5.2 mSv at 400 MBq and an effective equivalent-dose of 0.013 mSv/MBq. To block thyroid uptake, patients received a saturated solution of potassium iodine and an effective equivalent-dose of 3 times daily on four consecutive days, starting the day before uptake, patients received a saturated solution of potassium iodine and an effective equivalent-dose of 0.013 mSv/MBq. To block thyroid uptake higher than physiological activity [23]. $^{123}$I-mIBG uptake in the adrenal glands was considered as normal if it was mild and symmetric and if the glands were not enlarged [24]. Scans were considered positive if at least one malignant lesion (primary tumor or metastases) was seen, regardless of the number of foci. Because histological proof of metastatic lesions was unavailable in most patients, findings on combined cross-sectional imaging were used as the reference standards [23].

**PRRT with $^{90}$Y-DOTATOC or $^{177}$Lu-DOTATATE**

A positive finding in the $^{68}$Ga-DOTATOC-PET-scan was a prerequisite for PRRT. Normally, the $^{90}$Y-labelled SSTR compound was used as the first choice for PRRT. However, if individual lesions were smaller than 2 cm in diameter $^{177}$Lu-DOTA-TATE was preferred for PRRT. The individualized treatment regime applied at our department is also based on various patient related factors. Generally, we aim for 4 treatment cycles 10 weeks apart each. The intended standard accumulated activity for $^{177}$Lu-DOTATATE is 29.6 GBq (4 × 7.4 GBq; 800 mCi=4 × 200 mCi) and 16 GBq (4 × 4 GBq; 432 mCi = 4 × 108 mCi) for $^{90}$Y-DOTATOC- treated patients. In patients with advanced disease stages, older age, poor Karnofsky performance index and diminished organ function due to pre-treatment individual doses are adapted guided by individual parameters, so that severe intermittent side effects (Grade III and IV) of PRRT would be avoided. All patients were infused with 1500 ml mineral solution containing 25 g of L-lysine and 25 g L-arginine for kidney protection. The amino acids solution was infused over the course of 4 h starting at 30 min before infusion of the radiopharmaceutical via a separate line.

The reference standard for the clinical outcome after PRRT was based on follow-up controls with all available patient records including also laboratory parameters and the correlation of PET and CT/MRI findings according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) [25]. The keystone for validation was repeated CT of the chest and abdomen at 3 to 6-month intervals during the first year after finalization of PRRT. The findings were broken down into three categories: Partial Remission (PR), Stable Disease (SD) and Progressive Disease (PD). The Progression Free Survival (PFS) and Overall Survival (OS) was also calculated from the time of first therapy intervention.

**Dosimetry**

Dosimetry based on the MIRD principle was performed following the application of the first therapy cycle. OLINDA/EXM-based dosimetry was performed according to the information provided in the Supplement 1 [26]. The whole-body dosimetry was performed alongside the first therapy cycle of each patient; for each following
Table 1: Locally inoperable or metastasized paraganglioma.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Age at Initial Diagnosis/ Age</th>
<th>Sex (f/m)</th>
<th>Location of Lesions, Initial Diagnosis</th>
<th>Dosimetric Radiopharmaceutical</th>
<th>Therapy</th>
<th>Cumulative Activity (GBq)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Tumour Lesions, Dose [Gy/ GBq] Calculation for Therapeutic Radionuclide</th>
<th>Tumour Accumulated Dose [Gy]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31/39</td>
<td>f</td>
<td>2011 jugularis right and left</td>
<td>$^{111}$In-DOTATOC</td>
<td>$^{90}$Y-DOTATOC (01/2012-07/2012), 4 cycles$^{a)}$</td>
<td>16.25 SD</td>
<td>alive &gt;8 years</td>
<td>9.4</td>
<td>152.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62/80</td>
<td>m</td>
<td>1994 posterior cranial fossa, cervical and lung metastases</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>$^{177}$Lu-DOTATATE (04/2006-11/2006), 4 cycles$^{a, b)}$</td>
<td>26.25 11</td>
<td>78 (6.5 years)</td>
<td>6.2</td>
<td>235.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18/30</td>
<td>m</td>
<td>2006 paraaortal left, bone and lymph node metastases</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>$^{177}$Lu-DOTATATE (01/2014-09/2014), 4 cycles</td>
<td>11.52 unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>37/47</td>
<td>f</td>
<td>2009 jugularis right</td>
<td>$^{111}$In-DOTATOC</td>
<td>$^{90}$Y-DOTATOC (05/2008-02/2009), 5 cycles$^{a, d)}$</td>
<td>17.09 unknown</td>
<td>LTF</td>
<td>1.7</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>49/60</td>
<td>m</td>
<td>2008 paraaortal lymph node and bone metastases</td>
<td>$^{111}$In-DOTATOC</td>
<td>$^{90}$Y-DOTATOC (03/2015-11/2015), 4 cycles$^{a)}$</td>
<td>16.16 10</td>
<td>103 (8.6 years)</td>
<td>1</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>58/67</td>
<td>f</td>
<td>2011 jugularis left</td>
<td>np</td>
<td>$^{90}$Y-DOTATOC (08/2012-03/2013), 4 cycles$^{a)}$</td>
<td>16.44 SD</td>
<td>alive np np</td>
<td>np</td>
<td>np</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>18/28</td>
<td>m</td>
<td>2009 jugularis left</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>$^{177}$Lu-DOTATATE (10/2009-07/2010), 5 cycles$^{a)}$</td>
<td>24.68 SD</td>
<td>alive &gt;10 years from initial diagnosis</td>
<td>0.57</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>73/68</td>
<td>f</td>
<td>2004 jugularis and tympanicum left</td>
<td>$^{111}$In-DOTATOC</td>
<td>$^{90}$Y-DOTATOC (06/2014-11/2014), 3 cycles</td>
<td>6.33 unknown</td>
<td>alive &gt;15 years from initial diagnosis</td>
<td>8.2</td>
<td>51.9</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>69/82</td>
<td>f</td>
<td>2008 jugularis and carotidum right lung, lymph node and bone metastases</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>$^{177}$Lu-DOTATATE (01/2019-04/2019), 2 cycles$^{a)}$</td>
<td>8.49 SD</td>
<td>alive &gt;13 years from initial diagnosis</td>
<td>3.2</td>
<td>27.2</td>
<td></td>
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<tr>
<td>10</td>
<td>65/74</td>
<td>f</td>
<td>2010 carotidum right and left</td>
<td>np</td>
<td>$^{90}$Y-DOTATOC (08/2011-03/2012), 4 cycles</td>
<td>16 SD</td>
<td>alive &gt;9 years from initial diagnosis</td>
<td>np</td>
<td>np</td>
<td></td>
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<tr>
<td>11</td>
<td>71/73</td>
<td>f</td>
<td>2017 jugularis left</td>
<td>$^{111}$In-DOTATOC</td>
<td>$^{90}$Y-DOTATOC (08/2017-10/2017), 2 cycles</td>
<td>8.07 SD</td>
<td>alive &gt;2 years from initial diagnosis</td>
<td>11.6</td>
<td>93</td>
<td></td>
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<tr>
<td>12</td>
<td>61/70</td>
<td>m</td>
<td>2010 carotidum right and left lung, bone and lymph node metastases</td>
<td>np</td>
<td>$^{90}$Y-DOTATOC (05/2010-01/2011), 4 cycles</td>
<td>12.16 36</td>
<td>69 np np</td>
<td>np</td>
<td>np</td>
<td></td>
</tr>
</tbody>
</table>
cycle only a 24 h whole body scan was acquired.

Statistical analyses

Only descriptive statistics was performed. Values are presented as mean ± standard deviations.

Results

Locally inoperable or metastasized paraganglioma

From 19 patients with PGL, 13 patients received 90Y-DOTATOC and 4 patient’s 177Lu-DOTATATE PRRT. In 2 patients 111In-DOTATOC dosimetry indicated high tumor dose but one patient refused therapy (No. 17) (Table 1) and in the other patient (No.19) kidney dosimetry was unfavorable.

Therapy evaluation and dosimetry

Patients treated with 90Y-DOTATOC showed significant uptake of 68Ga-DOTATOC and received 111In-DOTATOC for dosimetry reasons along the 1st therapy cycle. No statistically significant difference in uptake of 90Y-DOTATOC was observed between PGL lesions and NET lesions (taken from our historic data) as demonstrated by the whole-body curves generated from the dosimetric calculations for 90Y-DOTATOC (Figure 1).

In 4/19 PGL patients, a negative 123I-mIBG scan was found despite of a highly positive 68Ga-DOTATOC PET. In fact, only one patient (Table 2, No. 5) showed a positive 123I-mIBG uptake but refused therapy with 131I-mIBG. This particular patient is still alive after more than 11 years of follow-up from initial diagnosis.

90Y-DOTATOC PRRT

From 19 patients with PGL, 13 patients received 90Y-DOTATOC PRRT in 1 to 4 cycles (Figure 2). In these patients, the accumulated activity ranged from 8.07 to 16.44 GBq (mean 13.6 GBq, median 16.16 GBq). The estimated accumulated tumour dose ranged between 4.6 and 152.8 Gy, (mean 51.1 Gy, median 38.3 Gy). In 6 patients, a SD was recorded by 68Ga-DOTATOC follow-up and 9/13 are still alive in 2020 after two to 15 years of follow-up.

In patient No. 5 with multiple lymph node and bone metastases, 90Y-DOTATOC therapy resulted in SD after 16.16 GBq (Figure 3). After progression of disease (PFS 10 months) high uptake was found for 123I-mIBG but the patient refused therapy with 131I-mIBG. Despite of slow disease progression, the patient is still alive in 2020 after >11 years of follow-up.

177Lu-DOTATATE PRRT

From 4/19 patients receiving 177Lu-DOTATATE, 2 patients were

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Table 2: Locally inoperable or metastasized paraganglioma - scintigraphy.

<table>
<thead>
<tr>
<th>123I-MIBG uptake</th>
<th>68Ga-DOTATOC uptake</th>
<th>18F-FDG uptake</th>
<th>18F-DOPA uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 negative</td>
<td>+++</td>
<td>/</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+++</td>
<td>+++</td>
<td>/</td>
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<td>3 /</td>
<td>+++</td>
<td>+++</td>
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<td>5 +++</td>
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<td>6 /</td>
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<td>14 negative</td>
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<td>17 /</td>
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<tr>
<td>18 negative</td>
<td>+++</td>
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</tr>
<tr>
<td>19 /</td>
<td>+++</td>
<td>/</td>
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</table>

np: not performed
* weak positive
** moderate positive
*** sufficient positive
/ not available
re-treated with another 4 cycles of $^{177}$Lu-DOTATATE (patients No. 2 and No. 3, Figure 4) which resulted in an absorbed tumour dose of 235.3 and 30 Gy, respectively. These 2 patients showed an OS of 78 and 103 months, respectively. The other 2 patients are still alive after ≥ 10 and 13 years of follow-up from initial diagnosis.

**Discussion**

Over the last 20 years PGL patients referred to our institution were evaluated by imaging with different radiopharmaceuticals. In summary, for staging or restaging our imaging data [9], suggest to use 1) $^{68}$Ga-SSTR targeting peptides as first choice for imaging 2) $^{18}$F-DOPA if $^{68}$Ga-SSTR targeting peptides are not available 3) $^{123}$I-mIBG in order to assess availability for $^{131}$I-mIBG therapy if PRRT is not feasible due to low or moderate uptake by the PGL lesions and 4) $^{18}$F-FDG to assess the prognosis for the disease. These recommendations are in line with the ENET’s guidelines which

**Figure 1:** Whole body retentions curves: Comparison of paraganglioma (n=12) and neuroendocrine tumor (n=10) patients receiving $^{90}$Y-DOTATOC PRRT.

$^{68}$Ga-DOTA-TOC PET/CT before and after PRRT with $^{90}$Y-DOTATOC (16.16 GBq) in a 74 year old patient with head/neck PGL (glomus tympanicum (red arrow), Table 2, No. 14). $^{111}$In-DOTATOC dosimetry estimated a tumor dose of 23.4 Gy.

**Figure 2:** Inoperable paraganglioma patient treated by $^{90}$Y-DOTATOC-PRRT.
suggest imaging by MRI and/or CT as well as by ⁶⁸Ga-SSTR PET/CT for suspected PGL without evident secondary lesions on CT [27].

Despite of the fact that PGL belong to the group of NETs that arise from tissues related to the autonomic nervous system, these tumors may show varying properties from the imaging point of view. In our group of patients with PGL all 19 patients showed a very intense SSTR-expression as assessed by ⁶⁸Ga-DOTATOC PET/CT but only one ¹²³I-mIBG positive scan results in five patients. We already published the high diagnostic value of ⁶⁸Ga-DOTA-TOC in PGL [10], and now we additionally show that the high uptake could be a valuable predictor for optional therapy with PRRT. ⁶⁸Ga-SSTR targeting PET-peptides are the most favorable imaging radiopharmaceuticals due to higher resolution over ¹²³I-mIBG SPECT imaging. Furthermore, due to the physiological biodistribution, the uptake of the radiopeptide is quicker (acquisition at 1 h post injection vs. 24 h for ¹²³I-mIBG) and the availability is higher due to in-house production. Future developments of mIBG-PET radiopharmaceuticals may provide superior imaging quality in this context.

Summing up our therapy results in this patient subgroup 17/19 patients were treated either with ¹⁷⁷Lu-DOTATATE or with ⁹⁰Y-DOTATOC, respectively: Nine patients are still alive and are in a good clinical condition despite metastatic spread.

What is the choice of treatment for patients with inoperable or metastasized paraganglioma? If a targeted therapy with radionuclides is an option, it is essential to consider which type of radionuclide is the best suitable. In principal, radionuclides decaying via α-, β- or auger-electron-emission are used and a certain amount of accompanying γ-emission is favorable for imaging purpose and dosimetry.

The "old" theragnostic concept provides evidence that ¹²³I-mIBG scintigraphy certainly has its place to select patients for ¹³¹I-mIBG therapy [13]. ¹³¹I-mIBG, which is similar to the body’s own catecholamines, is selectively been taken up and internalized by NET cells including pheochromocytoma and paraganglioma und thus irradiates the tumor cells with high specificity. Although the β-radiation of ¹³¹I has a lower tissue reach it thereby beneficially spares surrounding healthy tissue. In this context, it has to be mentioned that ¹³¹I-mIBG therapy is one of the most considerable treatments with unresectable and or metastatic PPGGL. However, no consensus about activity and frequency is available despite of preventing disease progression and symptom reduction.

The use of PRRT steadily is increasing worldwide since its approval by EMA and the FDA of ¹⁷⁷Lu-DOTATATE for GEP-NET in 2017 [15]. PGL are rare and thus not really of industrial interest and not found worth for approval yet. One would assume that NET patients, who have generally a larger tumour mass, would have a higher fraction of applied activity in the whole body. But as shown in Figure 1 no significant difference was found between NET-lesions and PGL-lesions concerning the whole-body retention curves of our patients.

Radionuclides have different radiopharmaceutical labeling capabilities and particle ranges. So shorter particle ranges are generally suitable for smaller-sized tumor lesions. This is also valid for ¹⁷⁷Lu as compared to ⁹⁰Y, because the smaller radiation ranges lead to better absorption of the emitted β-energy. On the other hand, the longer range of ⁹⁰Y (about 12 mm in tissue), may be beneficial to treat larger tumor lesions, which may also be less vascularized or have a heterogeneous receptor distribution. Due to the so-called “crossfire-effect”, tumor cells farther away from the receptor-bound radiopharmaceutical will receive an irradiation with therapeutic effect. In comparison to ¹⁷⁷Lu, ⁹⁰Y also exhibits a higher Linear Energy Transfer (LET). Radionuclides with higher LET will have a larger effect on the targeted tissue per decay. A shorter half-life will lead to higher absorbed dose rates. From a radiobiological standpoint, higher dose rates delivered over shorter treatment times are more effective than lower dose rates delivered over a longer period [28]. Due to the longer half-life of ¹⁷⁷Lu compared to ⁹⁰Y, the tumor cell population may have more time for proliferative regeneration, however.

We used both ⁹⁰Y- and ¹⁷⁷Lu-labeled SSTR-binding analogs in patients with PGL. As most of the PGL were rather large lesions the preferable SST analog used for therapy was ⁹⁰Y-DOTATOC. In
fact, we started PRRT when \(^{177}\)Lu-DOTATATE was not yet available and patients received the \(^{90}\)Y-compounds at our institution. The mean accumulated tumor dose for PGL lesions was approximately 50 Gy (by large variation) which resulted in stabilization of the disease in most patients after 3 therapy cycles with approximately 3.7 GBq \(^{90}\)Y-DOTATOC each. Obviously, this results in a rather low accumulated dose for most PGL lesions, whereas single lesions received an accumulated dose up to 230 Gy (Table 1, No. 2) which led to shrinkage.

As in other previous reports also the results (number of patients, therapy, and outcome) of our retrospective study are heterogeneous in this rather small cohort of patients suffering from a disease with a long-life expectancy [29]. In fact, approximately half of our patients (9/19) are still alive and progression free after many years of follow-up. Some patients with stable disease received multiple additional treatments including radiotherapy or local surgery in a multidisciplinary approach, so the PFS related to PRRT alone was difficult to estimate. Others reported a PFS between 21.6 [4] and 39 months. More importantly, in our long-term study the OS reached even decades.

A combination of \(^{90}\)Y/\(^{177}\)Lu to achieve control of both small and large lesions corresponding to the different tissue penetration of the emitted radiation is also possible [30]. Our data show that some patients may also benefit from re-PRRT at disease progression, if disease stability is obtained by the first period of PRRT (such as patient Table 1, Nr. 3, who showed an OS of 103 months).

The definition of PGL progression is a difficult issue. It is well known, that in many oncological settings, functional changes detected by PET can precede morphological changes on diagnostic CT, especially in case of bone lesions and small lymph nodes. However,
PET may fail to detect small lesions within the liver better detected by diagnostic CT or MRI [27]. RECIST criteria are not ideal for NETs since they rely on changes in the size of lesions, and this can especially be challenging in patients with slow-growing PGL [25].

One controversial issue in the management of PGL concerns the use of 18F-FDG in addition to 68Ga-DOTA-SSTR PET/CT to detect disease progression. Some retrospective studies investigated the impact of dual-tracer imaging in NET patients [22]; however, the data reported so far are controversial. 18F-FDG-positive lesions may still respond to PRRT as long as they are 68Ga-SSTR-positive. In our observation some PGL-patients showed 18F-FDG-positive lesions which were also SSTR-positive and the clinical outcome was not influenced negatively. Only in case of a mismatch pattern, meaning FDG-positive and SSTR-negative lesions, a worse prognosis was found (such as patient No. 7, 1 and 2). In this case other treatments than PRRT or combined treatment options should be considered. In fact, several of our PGL patients received additional treatments after PRRT in a multidisciplinary approach.

In summary, for this special disease tailored treatment schemes should be found in multidisciplinary tumor boards. Also, PRRT should be adjusted individually to achieve higher responses while reducing toxicity. Positron emission tomography can facilitate the use of radiopharmaceuticals but its utility is not yet in practice.

Conclusion

Both 177Lu- and 186W-SSTR-targeting peptides may be useful for long-term disease control in patients with locally advanced or metastatic paraganglioma. Pretherapeutic scanning for a tailored treatment regimen seems appropriate in order to identify the radiopharmaceutical with highest tumour uptake.

Ethics

The application of 177Lu-W- and 186W-SST analogues was approved by the institutional review tumor board and all patients gave written informed consent prior to therapy and imaging studies. All patients received radiolabeled peptides under compassionate use condition according to the updated Declaration of Helsinki, prepared according to the Austrian Medicinal Products Act, AMG§8 and §62. All regulations of the Austrian Agency for Radiation Protection were observed. Informed Consent According to the Austrian Laws, for this type of study, a formal consent is not required.

References


