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Title:

Peptide Receptor Radionuclide Treatment and (131)I-MIBG in the management of patients with metastatic/progressive Phaeochromocytomas and Paragangliomas.

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Short running title:

Radionuclide therapy of advanced PGL/PCC

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Synopsis:

Radionuclide treatment has been shown to be quite effective in the management of advanced paragangliomas and pheochromocytomas. Apart from I(131)-MIBG which has been used in the past, recently, peptide receptor radionuclide treatment (PRRT) has been

shown to be effective in the management of these tumors. We present series of patients showing their response to these treatments.

Abstract

Background and objectives: Radionuclide therapy has been used to treat patients with progressive/metastatic paragangliomas (PGLs) and phaeochromocytomas (PCCs). The aim of the present study is to retrospectively compare the therapeutic outcomes of these modalities in patients with progressive/metastatic PCCs and PGLs.

Methods: Patients with progressive/metastatic PGLs and PCCs that were subjected to radionuclide treatment in our department were retrieved from our department's database for the period 1998-2013. Overall survival (OS), progression free survival (PFS), event free survival (EFS) and response to treatment were calculated. Treatment toxicity was documented.

Results: Twenty two patients with progressive/metastatic PGLs or PCCs were treated with either (131)I-MIBG, (90)Y-DOTATATE or (177)Lu-DOTATATE. A total of 30 treatments were administered (16 treatments with (131)I-MIBG, 2 with (177)Lu-DOTATATE and 12 with (90)Y-DOTATATE. Patients treated with PRRT had increased PFS and response to treatment compared to (131)I-MIBG treated patients ($p<0.05$). However, difference in OS was non significant ($p=0.09$). There was no difference in major toxicities between groups. When comparing only patients with PGLs, OS, PFS, EFS and response to treatment were significantly higher in the PRRT treatment group.

Conclusion: PRRT treatment offers increased OS, PFS, EFS and response to treatment compared to (131)I-MIBG therapy in patients with progressive/malignant PGLs.

Keywords: radionuclide therapy, (131)I-MIBG, peptide receptor radionuclide treatment, phaeochromocytoma, paraganglioma,.

Introduction

Phaeochromocytomas (PCC) and paragangliomas (PGL) are tumors of chromaffin cells that often produce and secrete catecholamines and their metabolites. PCC occur within the adrenal medulla and PGL present as tumors of the extra-adrenal sympathetic nervous system, occurring in the head and neck, chest, abdomen, or pelvis [1]. These tumors can present either as benign, in the majority of the cases, or may be malignant.

There are currently no established criteria for establishing PCC/PGL as malignant apart from the presence of metastases at diagnosis [2]. In cases where metastases are found, surgery is usually of limited therapeutic value and other therapeutic modalities have been proposed. These include chemotherapy, external radiotherapy, radiofrequency ablation therapy, tyrosine kinase receptor inhibitors and radionuclide therapy [2-6].

(131)I-metaiodobenzylguanidine (MIBG) is a frequently used treatment for advanced neuroendocrine tumors, leading to symptomatic control, stabilization of disease progression and increased overall survival [7]. Peptide Receptor Radionuclide treatment (PRRT) with radiolabeled somatostatin analogues have also been used in the treatment of neuroendocrine tumors. However, data on PRRT use in metastatic PCCs and PGLs are limited. There are a few reports for the treatment of these patients with PRRT, and although this therapy seems effective, it is not reported to be as effective as in other subtypes of neuroendocrine tumors [8-10].

To date, there is no study comparing (131)I-MIBG treatment and PRRT in the management of patients with progressive PCCs and PGLs. The aim of the present study is to retrospectively compare MIBG and PRRT treatment in patients with

metastatic/progressive PCCs and PGLs, in terms of overall survival, progression free survival, event free survival, response to treatment, and toxicity.

Materials and Methods

Population

This was a retrospective study of the patients with locally advanced /metastatic progressive PGLs and PCCs treated in our department during the period 1998-2013. All patients were characterized as "metastatic" either during follow-up after initial surgery, or when metastases were present at tumor diagnosis.

The decision for commencement of radionuclide therapy was made in the Neuroendorine Tumour Multi-Disciplinary Team meeting and was based on either disease progression and/or failure to control symptoms of catecholamine hypersecretion. Patients were allocated to either (131)I-MIBG or PRRT treatment, according to their respective tumor avidities for (123)I-MIBG versus somatostatin receptor agonist tracers, either (111)In-diethylenetriaminepentaacetic acid (DTPA)-Octreotide or (68)Ga- tetraazacyclododecane tetraacetic acid octreotate (DOTATATE). Patients that had metastatic pheaochromocytomas were scanned for (123)I- MIBG avidity and then scanned for somatostatin analogue peptide avidity if there was no avidity or poor avidity to (123)I-MIBG. Patients with metastatic paragangliomas were checked for avidity to (123)I-MIBG and when negative for avidity to somatostatin receptor agonist tracers. In view of this patients in our series were not routinely scanned for both modalities throughout the

entire study period. However, during the years of the study period imaging with somatostatin receptor agonist tracers has increased in our department as a result of the increased avidity that has been shown in patients with PGLs.

Patients with non-progressive and symptomatically controlled disease, surgically treatable primary or metastatic disease, as well as patients with renal failure or bone marrow disease were excluded from radionuclide treatment.

Patient age, sex, tumor type, tumor location, genetic background, the presence of metastasis on diagnosis, the operability, the extent of metastatic disease, the functionality of the tumor and the administration of additional therapies were recorded.

As this was a retrospective audit of practice, research ethical approval was not required.

Radionuclide Therapy Protocol

(131)I-MIBG

All patients had a pre-therapy (123)I-MIBG scan to assess appropriate uptake of tracer in the sites of known disease. The administered activity of (123)I-MIBG was 220 MBq with scans performed on a dual-head gamma camera using a low-energy high-resolution collimator 24 h after injection.

Treatment was administered in a shielded side-room on the oncology ward. Patients underwent thyroid blockade with oral potassium iodide prior to treatment, starting on the day of the therapy and continued for a further 4 days after therapy. Ondansetron 8 mg orally was also given 30 min before the (131)I-MIBG to minimize nausea. Standard activity varied over the years. In patients treated after the year 2000, the standard activity administered was of 5.5 or 7.4 GBq of (131)I-MIBG (GE Healthcare, Amersham,

Buckinghamshire, UK) in two vials (5.5 GBq) or three vials (7.4 GBq). The standard protocol involved three cycles of (131)I-MIBG therapies with intervals of 10–12 weeks between each treatment. Fewer than three cycles were administered if there was any evidence of significant toxicity. Patients before 2000 were treated using two different regimes. Those with fast-growing tumours and significant symptoms were treated with three infusions of 131I-MIBG, given at 10- week to 12-week intervals. If there was evidence of response, the patients were then maintained on 6- monthly treatments. In those patients with more slowly growing disease, 6-monthly treatments were used from the outset.

Treatment was administered over approximately 40 min using a semi-automated delivery system (GE Healthcare, Amersham, Buckinghamshire, UK), with 90% of activity passing from the delivery system to the patient. Cardiovascular monitoring was routinely used during administration. Patients were closely observed from behind a lead shield during the administration. Patients were monitored by the hospital radiation safety group and discharged when their dose rate at 1 m had fallen to ≤600 MBq. Two to three days after treatment, a post-therapy whole-body scan was obtained on a dual-head gamma camera using a high energy general purpose collimator. This was performed to assess the biodistribution of the tracer.

PRRT

Treatment was administered in a shielded side-room on the oncology ward. Ondansetron 8 mg was injected intravenously and an infusion of amino acids containing lysine 25g and arginine 25g in 2 L 0.9% NaCl was started 30 minutes before the administration of the radiopharmaceutical and lasted 4 hours. The radiopharmaceutical [either (90)Y-

DOTATATE or (177)Lu-DOTATATE] was co-administered via a second pump system. Cycle activities given were 3.2 GBq for Y-90 DOTATATE and 7.4 GBq for Lu-177 DOTATATE, injected over 30 minutes. The standard protocol involved three to four cycles of therapies with intervals of 10–12 weeks between each treatment. Fewer cycles were administered if there was any evidence of significant toxicity.

Follow-Up

Patients' symptoms and adverse effects were evaluated after each cycle and overall 3 months following the completion of treatment courses. Routine haematology, liver, renal, and thyroid function tests, as well as tumour markers were performed before each therapy, as well as at follow-up visits. Follow up was discontinued only if the patient died or were assigned to palliative care, when only information concerning the patients' status were recorded.

Although biochemical and symptomatic response was evaluated with blood investigations and quality of life questionnaires (EORTC QLQ – GI.NET21), this was not done consistently and per protocol and as a result data were not eligible for retrospective collection and analysis.

Patients underwent restaging cross-sectional imaging (CT or MRI) between 6 weeks and 3 months after the completion of treatment courses and then every 4-6 months. Tumor response to treatment was evaluated retrospectively according to the RECIST 1.1 criteria. All imaging were reviewed by an experienced radiologist.

Progression free survival was defined as the interval between the first radionuclide treatment and the radiological progression of the disease, or death related to the disease.

Time to progression was also calculated and was defined as interval between the first radionuclide treatment and the radiological progression of the disease without taking death into account. Finally, as we did not have any consistent data on quality of life after the treatment, we calculated event free survival, which was defined as the interval between the first radionuclide treatment and any event related to radiological progression, major toxicity, any major disease related event that lead to hospitalization or death. As many patients were subjected to multiple treatments, progression free survival, time to progression, event free survival and response to treatment were calculated individually for every treatment and not per patient. Overall survival was calculated for every patient and was defined as the interval between the first radionuclide treatment and death.

Treatment toxicity

Minor side effects, during or after treatments, were not recorded. Data for major side effects of treatment, in terms of haematological and renal toxicity, were collected. Renal and haematological toxicity were graded, according to the National Cancer Institute Toxicity Criteria.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD). Comparison between groups was performed using the Chi-Square test for qualitative data and the unpaired t-test for quantitative data. Overall Kaplan–Meier survival curves, progression-free Kaplan–Meier survival curves, time to progression curves and event free survival curves were generated for each group and compared with a log-rank test for proportional hazards and the

Breslow test if differences were depicted early in the follow up period. A p value smaller than 0.05 was considered as significant.

Results

During the period 1998-2013 we found 22 patients with progressive metastatic paragangliomas or phaeochromocytomas that were referred for radionuclide therapy with either (131)I-MIBG, (90)Y-DOTATATE and (177)Lu-DOTATATE. The mean age at diagnosis was 46.9 ± 15 years. Patient characteristics are summarized in TABLE 1.

From the 22 patients receiving radionuclide treatment 8 patients received treatment with (90)Y-DOTATATE, 1 patient treatment with (177)Lu-DOTATATE, 11 patients treatment with (131)I-MIBG and 2 patients received a combination of the above treatments. A total of 30 treatments were administered in these patients. Analytically, these consisted of 16 treatments with (131)I-MIBG, 2 treatments with (177)Lu-DOTATATE and 12 treatment cycles of (90)Y-DOTATATE. The seven patients with PCCs were subjected to 9 treatments, 8 of which were with (131)I-MIBG and one with (90)Y-DOTATATE. The 15 with PGLs were subjected to 21 treatments, from which 13 were with PRRT and 8 were with (131)I-MIBG. The above data, cumulative dosage, treatment cycles and total number of treatments are summarized in TABLE 2.

Patients were followed up continuously in our departments' outpatient clinic. The follow-up period ranged from 6 to 122 months (mean 38.7 months) for patients that eventually died and 2 to 134 months (mean 56.4 months) for patients that were alive at the end of the study period. We had no patients lost in follow-up. Overall survival was compared between patients that received (131)I-MIBG or PRRT treatment, and thereafter between patients treated with (131)I-MIBG and (90)Y-DOTATATE. Only two patients received (177)Lu-DOTATATE, thus making the addition of an additional group not applicable. Overall survival was not different when comparing treatments with (131)I-MIBG versus

PRRT, or (131)I-MIBG versus (90)Y-DOTATATE (p=0.09 and p=0.08 respectively). Further stratification of the two treatment groups according to tumor type was made. All patients with progressive/metastatic PCCs were treated with (131)I-MIBG or a combination of (131)I-MIBG with PRRT (as per imaging avidity protocol) and as a result no comparison was made. Patients with progressive/metastatic PGLs had a longer overall survival when treated with PRRT or (90)Y-DOTATATE compared to (131)I-MIBG (p=0.01).

Progression free survival for all patients was longer in patients treated with (90)Y-DOTATATE compared with (131)I-MIBG (p=0.04), however, this difference was not statistically significant when comparing all PRRT treated patients (p=0.1). In patients with PGLs, progression free survival was longer after PRRT or (90)Y-DOTATATE treatment compared to patients treated with (131)I-MIBG (p=0.01 and p= 0.007, respectively). There were no differences in time to progression or event free survival between these treatment groups, when including all patients. However, in patients with PGLs, event free survival was longer both after (90)Y-DOTATATE (p=0.02) or any PRRT treatment (p=0.04), compared with patients treated with (131)I-MIBG. Data are summarized in TABLES 3 and 4 and FIGURE 1 and 2.

Response to treatment, as determined by RECIST 1.1 criteria, was significantly better after PRRT, in general, and after (90)Y-DOTATATE treatment compared to (131)I-MIBG treated patients (p= 0.013 and p=0.021 respectively). When comparing patients with PGLs separately, response to treatment was also higher when comparing either PRRT, in general, or (90)Y-DOTATATE treatment specifically with (131)I-MIBG treated patients (p=0.005 and p=0.008, respectively).

Six patients (27.2%) developed renal impairment during their follow up. However, not all of these toxic events were related to the radionuclide treatment. In one case renal impairment was due to ureteric obstruction from the tumor and in another case renal impairment was secondary to NSAID treatment after a metastatic fracture. When these cases were excluded, only 4 (18.1%) patients developed renal toxicity related to radionuclide treatment, of which only 2 (9%) were serious (Grade 3 or 4). One of the patients was treated with PRRT, while the other one was treated with a combination of (131)I-MIBG and PRRT. Nine (40.9%) patients had haematological complications during their follow up, but only 5 cases (22.7%) could be attributed to radionuclide treatment. There was no difference in haematological toxicity between patients treated with (131)I-MIBG and patients treated with (90)Y-DOTATATE therapy. Both renal and haematological side effects are summarized in Table 5.

Discussion

The management of patients with metastatic PCCs and PGLs can be challenging. Although multiple therapeutic modalities exist, including chemotherapy, external beam radiation, tyrosine kinase inhibitors and surgery in some cases, radionuclide treatment has been shown to be most effective in the treatment of those patients [10-12]. Traditionally, (131)I-MIBG has been shown to have a high tracer affinity for these tumors [13]. During the last decades, radionuclide imaging with radiolabeled somatostatin analogues has been shown to be an alternative option, as well, leading to respective therapeutic interventions [8]. (90)Y-(DOTATOC), (90)Y-DOTATATE and (177)Lu-DOTATATE are the main

peptide receptor radionuclide treatment used to date [8-10,14]. The literature is scarce in studies comparing these two agents in neuroendocrine tumors in general, while there is no study to date comparing these treatment modalities in metastatic/progressive PCCs/PGLs.

In our study, most of the PRRT treatments used (90)Y-DOTATATE, with the exception of two patients that received (177)Lu-DOTATATE (one as a monotherapy and one as an additional treatment cycle after previous (131)I-MIBG treatment). This was due to the fact that (177)Lu-DOTATATE was not available in our department during the entire data collection period, and became available after 2011.

Patients with metastatic PCCs were treated mainly with (131)I-MIBG. On the contrary, patients with metastatic PGLs were treated either with (131)I-MIBG or PRRT, mostly with (90)Y-DOTATATE. This can be explained by the fact that patients with PCCs were mostly (123)I-MIBG avid. The opposite was true for patients with PGLs, where there was increased avidity for somatostatin receptor radionuclide imaging. During the last decades diagnostic imaging strategies have changed significantly for these two tumors. Traditionally these tumors were both imaged with MIBG, until a significant percentage of PGLs and some PCCs were found to be avid to (111)In- (DTPA)-Octreotide scan and even bigger percentage avid to (68)Ga- (DOTATATE) PET. In view of this the imaging protocol of these patients in our department has evolved as well during the study period. This is in accordance with the literature [15-18].

Overall survival was not significantly different when comparing (131)I-MIBG and PRRT treatments in the entire study population. However, when only patients with PGLs were compared, there was a difference in overall survival between the treatment groups. The

difference in our results when stratifying for tumor type can be interpreted by a difference in the efficacy of the two treatment modalities.

The two treatment modalities were also compared in PFS, TTP, EFS and response to treatment. Our results show that PRRT seems to be more effective than (131)I-MIBG in terms of response to treatment, but with no difference in PFS, TTP and EFS in patients with metastatic PGLs and PCCs. However, when comparing only patients treated with (90)Y-DOTATATE, they had increased response to treatment, as well as PFS.

Very few studies have addressed the effect of PRRT in the management of patients with metastatic PGLs and PCCs. Recently, Forrer reported an overall response to treatment in 22 of 28 (78%) patients, with a PFS ranging from 3 to 43 months [8]. Prasad et al also reported the results of PRRT [(90)Y-DOTATATE, (177)Lu-DOTATATE and combination] in 20 patients with progressive PGLs and PCCs. They reported an 80% and 43% overall response rate with (177)Lu-(DOTATATE and (90)Y-DOTATATE treatment, respectively. Best results were reported after combination treatment [9]. Recently, Puranik et al reported a series of 9 patients with inoperable head and neck paragangliomas treated with PRRT. They demonstrated disease stabilization and symptomatic relief of these patients after treatment. However, theirs study did not concern metastatic disease as only one of the nine patients had distant metastasis [10].

In our study, we have shown a response in 11 of 11 (100%) treatments with (90)Y-DOTATATE and a mean PFS of 43 months. However, this result should be interpreted with caution, as one of the patients in this group had initially presented with a locally inoperable and symptomatic PGL, received radionuclide treatment and later developed metastases. In addition, in our study, response to treatment was evaluated 6 weeks to 3

months after treatment and according to RECIST 1.1 criteria, as opposed to WHO and other criteria used in other studies [7].

Radionuclide treatment with (131)I-MIBG has been better studied in patients with progressive/malignant PCCs and PGLs. Recently, Gonias et al reported a phase II prospective study of 50 patients with malignant disease that were treated with high dose (131) MIBG. In their study, they reported 27% response to treatment and 80% non-progressive disease with radiologic criteria after the first treatment. In our study we observed 62.5% non- progressive disease after (131)I-MIBG treatment sessions. However, in their study they evaluated response rate 3 to 6 months after the treatment, in contrast to our study, where the response rate was evaluated 6 to 12 weeks after treatment. In addition, in their study, they incorporated patients receiving a higher dose protocol for (131)I-MIBG, compared to our study. Fitzgerald et al also reported an initial 83 % overall response rate after high dose (131)I-MIBG treatment in patients with PGLs and PCCs. Some patients showed progression later in their follow up and the overall response rate became 66%[1].

An interesting finding in our study is that efficacy of treatment seems to be different between patients with PCCs and PGLs, suggesting that these two pathologies should probably not be treated similarly. PRRT was found to be of no benefit to OS, OFS, EFS and TTP compared to (131)I-MIBG when including all the patients in the analysis. However, there was a clear benefit in terms of response to treatment. One could argue that PCC patients were only treated with (131)I-MIBG or a combination of (131)I-MIBG and PRRT and these patients have been reported to have worse prognosis that patients with PGLs, thus effecting our results. However, we noted a clear difference in overall

survival, PFS, EFS and response to treatment in favor of PRRT when comparing only patients with metastatic PGLs, as opposed to incorporating PCCs in the comparison. A similar comparison could not be made for PCC patients due to the retrospective nature of the study, as all patients with PCCs were treated with (131)I-MIBG or a combination of (131)I-MIBG and PRRT. It is possible that PCCs and PGLs have a different response to (131)I-MIBG or PRRT. Chen et al have shown that somatostatin receptor scintigraphy is more sensitive than (131)I-MIBG imaging in the detection of extra-adrenal phaeochromocytomas using (99m)Tc-HYNIC-TOC as a tracer [15]. In the same time, Koopmans et al have reported similar data for the affinity of head and neck paragangliomas using (111)In-octreotide vs (123)I-MIBG [16]. In keeping with this, Jalil et al has reported a sensitivity of 88% for the detection of unilateral PCCs as opposed to 64% for extra adrenal tumors using (131)I-MIBG scintigraphy [19]. Bhatia et al have published similar results (85% for PCCs and 58% for PGLs) with (123)I-MIBG scintigraphy.

The single most important finding of our study was that patients with metastatic PGLs seem to have a better prognosis when receiving PRRT treatment instead of (131)I-MIBG. In view of this it seems more rational that these patients be preferentially scanned for somatostatin receptor agonist tracer avidity and only when no avidity is found, for (123)I-MIBG avidity. However, the same cannot be said for patients with metastatic PCCs, direct comparison between the two treatments could not be made in our study.

A major limitation of our study includes the retrospective nature of the data collection. In addition, the PRRT group included only a small number of patients treated with (177)Lu-DOTATATE, since it has only been available in our unit since 2011. In the (131)I-MIBG

treatment group dosage protocols varied during the period studied and as a result, there is heterogeneity in the treatment protocol between patients. Our unit's protocols did not include high dosage treatments, which has been reported to be quite effective in neuroendocrine tumors in general and PGLs/PCCs in particular. Recent data have also speculated the role of a combination of these treatment modalities, in order to be able to maximize efficiency and limit toxicity, which we did not address in our study [20,21]. Finally, we did not have comparative data on symptomatic/biochemical response or quality of life after the above treatments in these patients. Prospective studies, preferably with stratification of cohorts for tracer avidity and utilizing (177)Lu-DOTATATE as the current standard of treatment for PRRT, are required to address these limitations and to confirm or refute our conclusions.

Conclusion

This is the first comparative study between radionuclide treatments for patients with metastatic/progressive PGLs and PCCs. These patients are usually studied as a group in most studies. Our study has shown superiority of PRRT compared to (131)I-MIBG treatment in these patients, with a pronounced effect when comparing PGL patients alone. Comparative data and results in our study seem to rely mostly on patients with progressive/malignant PGLs. Although the mainstream therapy for progressive/malignant PCCs is (131)I-MIBG, there might be a benefit from PRRT treatment as well. This should be addressed in future prospective trials.

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Figure legends

Figure 1

Kaplan Meier Curves comparing Overall Survival, Progression Free Survival and Event Free Survival between patients with Paragangliomas and Phaeochromocytomas treated with a) (131)I-MIBG vs PRRT and b) (131)I-MIBG vs (90)Y-DOTATATE.

(* $p<0.05$)

Figure 2

Kaplan Meier Curves comparing Overall Survival, Progression Free Survival and Event Free Survival only in patients with Paragangliomas treated with a) (131)I-MIBG vs PRRT and b) (131)I-MIBG vs (90)Y-DOTATATE.

(* $p<0.05$)

Table 1 Characteristics of patients treated with radionuclide therapy

Case	Age	Sex	Tumor	Genetic Testing	Metastatic at diagnosis	Extent of Disease prior to radionuclide treatment	Clinically Functioning Tumor	Mitosis index
1	56	M	Phaeo	-	No	Liver	Yes	N/A
2	71	F	Para	-	Yes	Liver	Yes	<1%MIB-1 staining
3	41	M	Para	-	No	Lungs, Liver, Lymph nodes	No	3 mitoses per 10hpf
4	39	M	Para	SDH-B	Yes	Bones	No	N/A
5	7	F	Para	-	No	Liver, Lymph Nodes	Yes	N/A
6	56	F	Para	-	Yes	Bones	Yes	1-5% MIB-1 staining
7	43	M	Phaeo	-	Yes	Bones	No	N/A
8	59	M	Phaeo	-	No	Liver, Bone	Yes	N/A
9	51	F	Phaeo	-	Yes	N/A	No	N/A
10	63	M	Phaeo	-	No	Lung, Lymph nodes	Yes	10% Ki-67 staining
11	49	F	Para	SDH-B	Yes	Liver, Bone, Lymph Nodes	Yes	N/A
12	29	M	Para	-	No	Lungs, Bone, Liver, Lymph Nodes	Yes	N/A
13	65	M	Para	-	No	Bones	No	15-20% staining
14	57	M	Para	-	Yes	Bones, Lymph nodes	No	30% Ki-67 staining
15	44	F	Para	-	No	Bones	Yes	N/A
16	40	M	Para	SDH-B	Yes	Bones, Liver	Yes	50% Ki-67 staining
17	42	F	Para	-	No	*, Bones	No	1% MIB-1 staining
18	35	M	Para	SDH-B	Yes	Lymph nodes, Soft tissue	Yes	N/A
19	68	F	Phaeo	-	No	Lung, Liver, Lymph nodes	No	10% MIB-1 staining
20	29	F	Para	SDH-B	Yes	Liver, Lymph nodes	No	5-10% MIB-1 staining
21	36	F	Para	-	No	Bones	Yes	<5% Ki67 staining
22	52	F	Phaeo	-	No	Lungs, Soft tissue, Intraperitoneal, Liver, bones	Yes	N/A

M= Male, F= Female, Para= Paraganglioma, Phaeo= Phaeochromocytoma, N/A= non available, SDH-B= Succinate dehydrogenase B

* Treatment due to incomplete resection (inoperable) / Progression. Bone metastasis developed during follow-up.

Table 2 Radionuclide and additional treatment to patients with progressive Paragangliomas/Phaeochromocytomas.

Case	Treatment	Treatment cycles	Total Number of Treatments	Cumulative Activity (MBq)	Somatostatin analogue treatment	Additional Treatment
1	(131)I-MIBG	1	3	16319	No	Chemotherapy (oxaliplatin capecitabin)
2	(131)I-MIBG	1	1	3200	No	-
3	Comb((131)I-MIBG/(90)Y-DOTATATE)	3	8	25644	Yes	External Radiotherapy
4	(90)Y-DOTATATE	1	3	7780	No	Chemotherapy (CVD)
5	(131)I-MIBG	1	3	15436	No	-
6	(90)Y-DOTATATE	1	3	3600	No	Samarium Nuclide Therapy
7	(131)I-MIBG	1	5	13000	No	-
8	(131)I-MIBG	1	3	22779	No	Chemotherapy (CVD)
9	(131)I-MIBG	1	3	N/A	No	-
10	(131)I-MIBG	3	10	66436	No	External Radiotherapy
11	(177)Lu-DOTATATE	1	3	N/A	No	External Radiotherapy, Chemotherapy (CVD)
12	Comb ((131)I-MIBG, (177)Lu-DOTATATE)	2	4	28400	No	Extrernal Radiotherapy
13	(131)I-MIBG	1	3	16201	No	Extrernal Radiotherapy, Chemotherapy
14	(90)Y-DOTATATE	2	5	14621	Yes	-
15	(131)I-MIBG	1	3	6323	No	-
16	(131)I-MIBG	2	4	14917	Yes	Metastasectomy, External Radiotherapy, Chemotherapy (cisplatin)
17	(90)Y-DOTATATE	1 (3)*	4	5680 (11361)	No	Metastasectomy
18	(90)Y-DOTATATE	1	3	9177	No	-
19	(131)I-MIBG	1	3	15592	No	Chemotherapy (CVD)
20	(90)Y-DOTATATE	1	3	9427	Yes	-
21	(90)Y-DOTATATE	2	6	17717	No	Radiotherapy
22	(90)Y-DOTATATE	1	1	7256	No	-

N/A: Not Available, CVD: Cisplatin, Vinblastine, Dacarbazine Chemotherapy

*Patient initially treated for locally advanced symptomatic disease. Second and 3rd single treatment cycles were given for symptom palliation and not for progression of disease.

Table 3 Therapeutic outcomes in patients with PCCs and PGLs

All patients	(131)I-MIBG	PRRT	P value (compared to (131)I-MIBG)	(90)Y-DOTATATE	P value (compared to (131)I-MIBG)
Overall Survival (months)	41.2±10.4	60.8±11.1	0.09	65.8±12.2	0.08
Progression Free Survival (months)	20.6±3.4	38.5±9.4	0.10	43.2±10.8	**0.04 ***
Event Free Survival (months)	22±5	17.9±2.8	0.39	18.9±3	0.54
Response to Treatment (Non progressive disease)	10/16 (62.5%)	13/13 (100%)	**0.013 ***	11/11 (100%)	**0.021***

* P statistically significant

Table 4 Therapeutic outcomes in patients with PGLs

PGL patients	(131)I-MIBG	PRRT	P value (compared to (131)I-MIBG)	(90)Y-(DOTATOC)	P value (compared to (131)I-MIBG)
Overall Survival (months)	22.8±6.3	60.8±11.1	**0.012 ***	65.8±12.2	**0.011 ***
Progression Free Survival (months)	14.4±2.9	38.5±9.4	**0.018 ***	43.2±10.8	**0.007 ***
Event Free Survival (months)	9.2±2.9	17.9±2.8	**0.042***	18.9±3	**0.022 ***
Response to Treatment (Non progressive disease)	4/8 (50%)	13/13 (100%)	**0.005 ***	11/11 (100%)	**0.008 ***

* P statistically significant

Table 5 Haematological and Renal complication in patients with metastatic paragangliomas and phaeochromocytomas.

Case	Treatment	Renal toxicity	Cause of toxicity	Haematological Toxicity	Cause of toxicity
1	(131)I-MIBG	-	N/A	Neutropenia (Grade 1)	Chemotherapy for bowel cancer
2	(131)I-MIBG	Grade not available	Renal obstruction from tumor	Thrombocytopenia (Grade 1), Anaemia (Grade 3)	Radionuclide treatment
3	Comb((131)I-MIBG/(90)Y-DOTATATE	Grade 3	Radionuclide treatment	Neutropenia (Grade 2), Lymphocytopenia (Grade 4)	Radionuclide treatment
4	(90)Y-DOTATATE	-	N/A	Neutropenia (Grade 3), Thrombocytopenia (Grade 4)	Chemotherapy (CVD)
5	(131)I-MIBG	-	N/A	-	N/A
6	(90)Y-DOTATATE	Grade 1	Radionuclide treatment	Anaemia (Grade 2), Thrombocytopenia (Grade 3)	Radionuclide treatment, Bone marrow tumor infiltration
7	(131)I-MIBG	-	N/A	-	N/A
8	(131)I-MIBG	-	N/A	Leukopenia (Grade 2)	Chemotherapy (CVD)
9	(131)I-MIBG	-	N/A	-	N/A
10	(131)I-MIBG	Grade 1	Radionuclide treatment	Leukopenia (Grade 2), Anaemia (Grade 2)	Radionuclide treatment
11	(177)Lu-DOTATATE	-	N/A	Thrombocytopenia (Grade 2)	Radionuclide treatment
12	Comb [(131)I-MIBG, (177)Lu-DOTATATE]	Grade not available	NSAIDS after metastatic fracture	-	N/A
13	(131)I-MIBG	-	N/A	Anaemia (Grade 2), Leukopenia (Grade 2) Thrombocytopenia (Grade 2)	Monosomy 7
14	(90)Y-DOTATATE	-	N/A	-	N/A
15	(131)I-MIBG	-	N/A	-	N/A
16	(131)I-MIBG	-	N/A	-	N/A
17	(90)Y-DOTATATE	Grade 2	Radionuclide treatment	-	N/A
18	(90)Y-DOTATATE	-	N/A	-	N/A
19	(131)I-MIBG	-	N/A	-	N/A
20	(90)Y-DOTATATE	-	N/A	-	N/A
21	(90)Y-DOTATATE	-	N/A	-	N/A
22	(90)Y-DOTATATE	-	N/A	-	N/A

N/A: Non Applicable

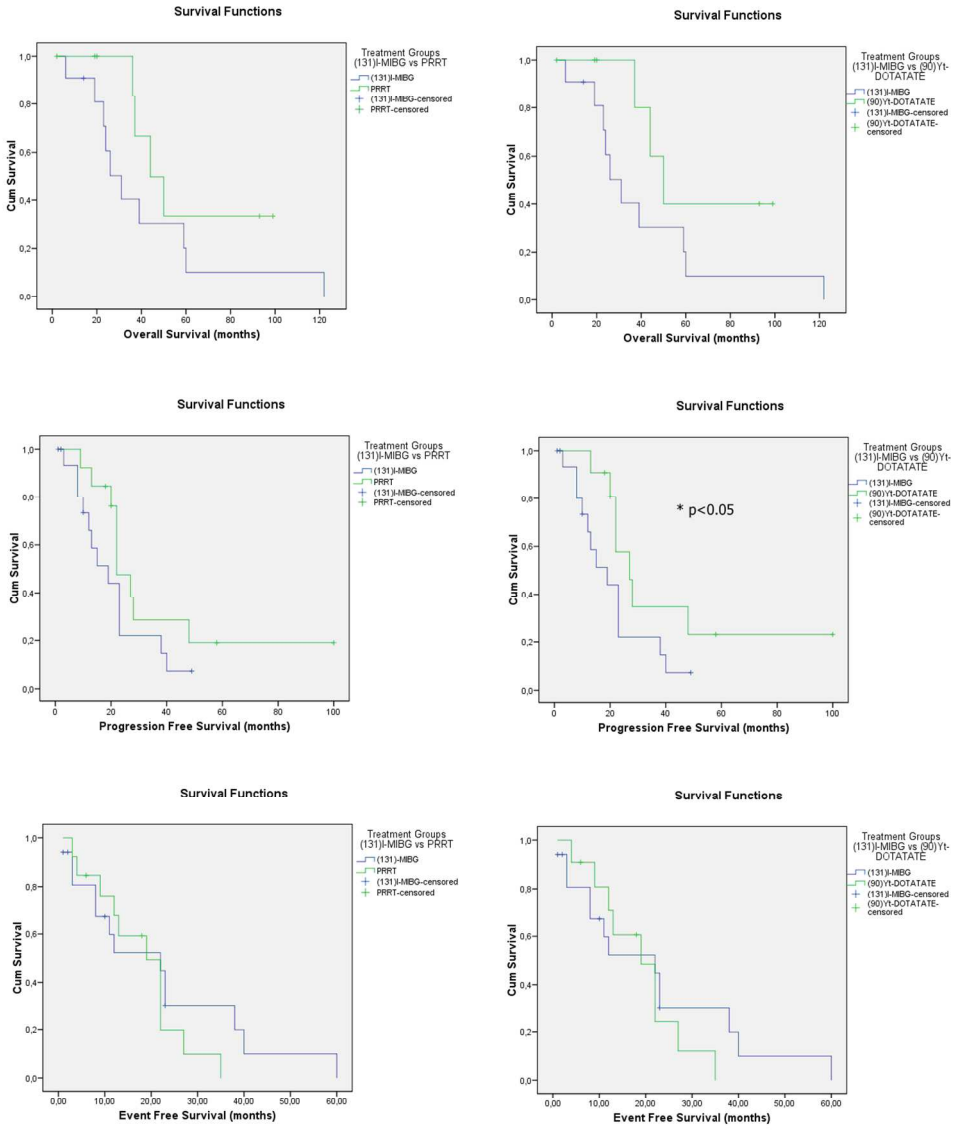

Figure 1

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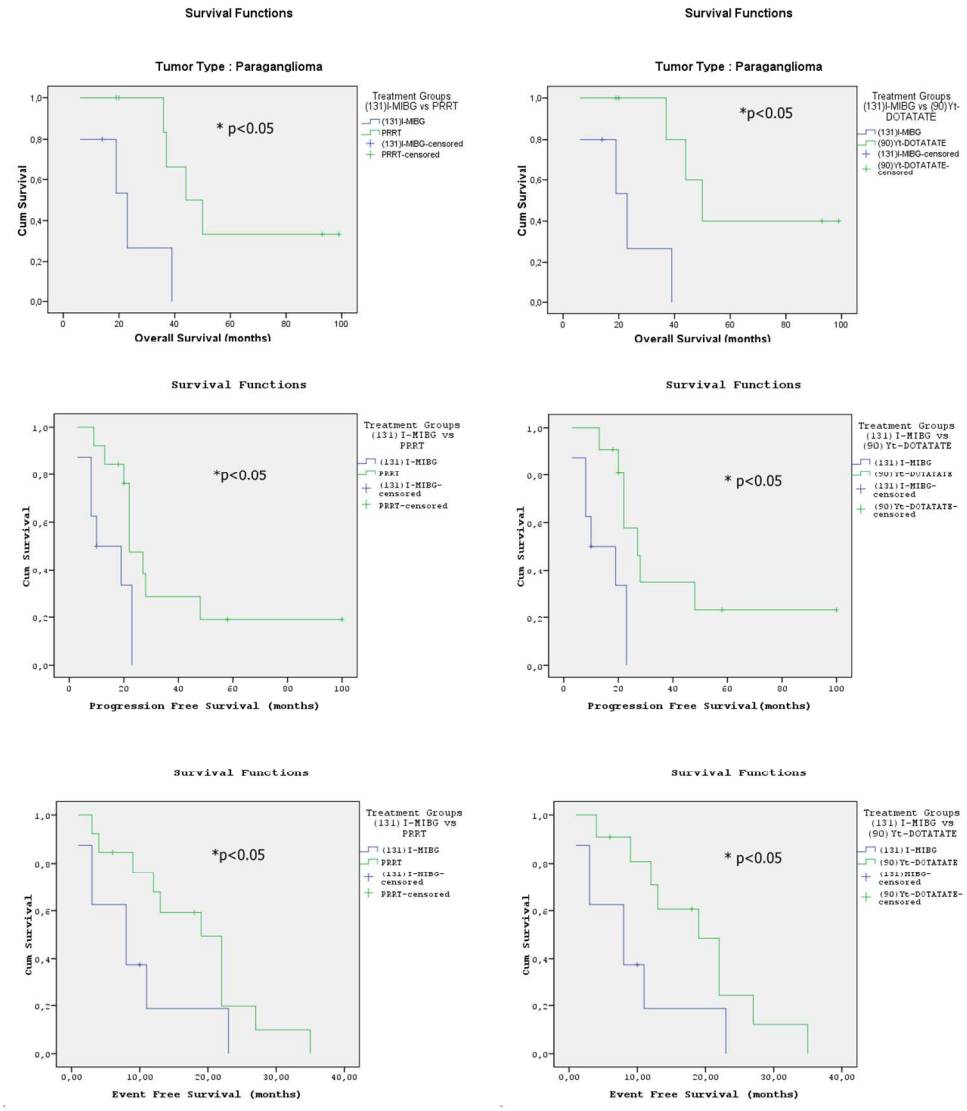

Figure 2

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