Peptide receptor radionuclide therapy of treatment-refractory metastatic thyroid cancer using $^{90}$Yttrium and $^{177}$Lutetium labeled somatostatin analogs: toxicity, response and survival analysis

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Abstract: The overall survival rate of non-radioiodine avid differentiated (follicular, papillary, medullary) thyroid carcinoma is significantly lower than for patients with iodine-avid lesions. The purpose of this study was to evaluate toxicity and efficacy (response and survival) of peptide receptor radionuclide therapy (PRRT) in non-radioiodine-avid or radioiodine therapy refractory thyroid cancer patients. Sixteen non-radioiodine-avid and/or radioiodine therapy refractory thyroid cancer patients, including follicular thyroid carcinoma ($n = 4$), medullary thyroid carcinoma ($n = 8$), Hürthle cell thyroid carcinoma ($n = 3$), and mixed carcinoma ($n = 1$) were treated with PRRT by using $^{90}$Yttrium and/or $^{177}$Lutetium labeled somatostatin analogs. $^{68}$Ga somatostatin receptor PET/CT was used to determine the somatostatin receptor density in the residual tumor/metastatic lesions and to assess the treatment response. Hematological profiles and renal function were periodically examined after treatment. By using fractionated regimen, only mild, reversible hematological toxicity (grade 1) or nephrotoxicity (grade 1) were seen. Response assessment (using EORTC criteria) was performed in 11 patients treated with 2 or more (maximum 5) cycles of PRRT and showed disease stabilization in 4 (36.4%) patients. Two patients (18.2%) showed partial remission, in the remaining 5 patients (45.5%) disease remained progressive. Kaplan-Meier analysis resulted in a mean survival after the first PRRT of 4.2 years (95% CI, range 2.9-5.5) and median progression free survival of 25 months (inter-quartiles: 12-43). In non-radioiodine-avid/radioiodine therapy refractory thyroid cancer patients, PRRT is a promising therapeutic option with minimal toxicity, good response rate and excellent survival benefits.

Keywords: Peptide radionuclide receptor therapy, non-radioiodine-avid, thyroid cancer, somatostatin receptors, survival analysis, $^{68}$Ga-DOTA-TOC, $^{68}$Ga-DOTA-TATE, positron emission tomography (PET)

Introduction

Differentiated non-medullary (follicular and papillary) thyroid carcinoma (DTC) usually has a good long-term prognosis with a 10-year survival rate of 85% to 99% [1, 2]. However, tumor recurrences occur in about 20% of patients, sometimes decades after initial therapy. Radioactive iodine is used for the detection ($^{123}$I, $^{131}$I) and treatment ($^{131}$I) of recurrent DTC, but 20% to 30% of recurrent tumors do not concentrate radiiodine [3, 4]. Hurthle cell thyroid carcinomas (HCCs), assigned to the group of follicular thyroid carcinomas, rarely take up iodine, even at the time of first diagnosis [5]. Additionally, iodine-avidity of metastases is a very important prognostic factor. The overall survival rate of patients with non-radioiodine-avid DTC is significantly lower than of patients with iodine-avid lesions [3, 6, 7]. Available well studied therapeutic and diagnostic options for this group of patients as well as patients with medullary thyroid carcinomas (MTC) are limited and studies on the effectiveness of chemotherapy, external beam radiation therapy and surgery are disappointing [6-9]. Consequently, various alternative approaches have been investigated for the diagnosis and treatment of
patients with non-radiiodine-avid DTC and medullary thyroid carcinoma [6, 7, 10, 11].

Several studies have demonstrated the involvement of somatostatin receptor (SSTR) family in the regulation of normal and tumoral thyroid cell proliferation [12] and thyroid tumor cell lines have shown to be SSTR positive [8, 13-15]. Based on these findings, the utilization of different types of radiolabeled somatostatin analogs have been suggested for therapeutic and diagnostic purposes in the management of MTC and non-radiiodine-avid DTC. $^{68}$Ga ($^{68}$Gallium)-DOTA (1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid)-Somatostatin Receptor (SMS-R) positron emission tomography (PET)/CT has been suggested as an alternative imaging modality [16, 17]. The therapeutic efficacy of $^{111}$In-octreotide, $^{90}$Y-DOTATOC ([(90Y-DOTA)$^3$,Tyr$^3$]-octreotide), $^{90}$Y-DOTA-lanreotide, and $^{177}$Lu-DOTA-TATE ([(177Lu-DOTA)$^6$,Tyr$^3$]-octreotate) have also been studied in some series [6-8, 10, 11, 18].

We report here the results of long-term follow-up in 16 non-radiiodine-avid thyroid cancer patients treated with $^{90}$Y/$^{177}$Lu-DOTA-TATE. Additionally, we discuss the application and role of $^{68}$Ga DOTA-Somatostatin Receptor (SMS-R) PET/CT as imaging modality in non-iodine-avid refractory thyroid cancer patients who have undergone peptide receptor radionuclide therapy (PRRT).

Materials and methods

Between 2004 and 2010, 16 patients with histopathologically proven non-radiiodine-avid refractory thyroid cancer with widespread distant metastases were referred for peptide-receptor radionuclide therapy to our European Neuro Endocrine Tumor Society (ENETS) Center of Excellence (Zentralklinik Bad Berka). There were 8 medullary thyroid carcinoma patients, 4 patients with follicular thyroid carcinoma, 3 Hürthle cell carcinoma patients, and one case with mixed carcinoma (follicular and medullary mixed carcinoma).

They were treated with peptide receptor radionuclide therapy (up to 5 times) in our center. Injected activities (dose) ranged from 2500-5000 MBq/per cycle for $^{90}$Y-DOTATATE and from 3500-7500 MBq/cycle for $^{177}$Lu-DOTATATE, respectively. Primary end points were treatment response and toxicity; the secondary end point was overall survival. Comprehensive relevant clinical information was gathered from the referred medical profiles and during follow-up periods (until death) at our center. Written informed consent was obtained from all patients in accordance with German regulations concerning the administration of radiolabeled substances to humans and documentation of the data in a database was approved by the patients and the local ethics committee.

Radiopharmaceutical

$^{68}$Ga was eluted from a $^{68}$Ge/$^{68}$Ga generator (obtained from Eckert and Ziegler, Berlin, Germany). The processing of this generator was developed on the basis of cation-exchange chromatography in hydrochloric acid/acetone media, which was rapid, simple, and chemically efficient. It successfully allows the purification and concentration of $^{68}$Ga [19]. Labeling of the peptides (DOTA-TOC, DOTA-NOC (1-Nal$^3$-octreotide), DOTA-TATE) was performed as mentioned in detail elsewhere [17, 18].

$^{68}$Ga DOTA-somatostatin receptor (SMS-R) PET/CT studies

$^{68}$Ga DOTA-SMS-R PET/CT was performed as described in detail elsewhere [16, 20, 21]. A dual-modality PET/CT (Biograph duo; Siemens Medical Solutions, Erlangen, Germany) was used, which consists of a PET system with a full-ring lutetium oxyorthosilicate (LSO) and a CT component corresponding to a Somatom Emotion Duo (Siemens Medical Solutions), a 2-row spiral CT system with a maximum continuous scan time of 100 s and a maximum rotation speed of 75 rpm. First, a CT was acquired over 1,024 mm axially. Coaxial whole-body imaging ranges were defined on the CT, covering an area from the skull to the upper thighs (6-7 PET bed positions, or 90-110 cm, depending on the size of the patient). CT was performed in spiral mode using a continuous acquisition at 130 kVp, 115 mAs, 4 mm collimation, 5 mm slice width, a table feed of 8 mm per rotation at 0.8-s rotation time, and 2.4 mm slice spacing. During the CT acquisition a limited breath hold protocol was followed which required the patients to hold their breath in normal expiration. After completion of the CT, patients were moved automatically to the PET toward the rear of the gantry, where 3-dimensional PET emis-
Table 1. Patients’ characteristics, baseline data, and status after the last PRRT

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<th>Age at 1st PRRT</th>
<th>Previous treatments</th>
<th>Dose of I-131 (GBq)</th>
<th>Σ PRRT</th>
<th>Metastases prior to PRRT</th>
<th>Status after last PRRT</th>
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<td>lung, LN</td>
<td>PD (died at 78)</td>
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</table>

*: excluded from progression survival analysis, m: male; f: female; N/A: not available, T: thyroidectomy; TT: total thyroidectomy; ST: strumectomy; ND: neck dissection; RT: external radiation; RIT: radioiodine therapy; C: chemotherapy; REDIFF: trial of redifferentiation using Roaccutan; LITT: laser-induced thermotherapy. LN: lymph node. SD: stable disease; PR: partial remission; PD: progressive disease; MP: minor progression; PD: progressive disease.
sion scanning subsequently started in the caudocranial direction with the bladder/pelvis region being scanned first. An emission scan time of 2-3 min per bed position was used for all patients which resulted in a total emission scan time of no more than 24 min and a total PET/CT examination time of about 30 min (including patient positioning, CT and PET imaging). The CT transmission images were used for attenuation correction of the PET emission data. After scatter and attenuation correction, PET emission data were reconstructed using an attenuation-weighted ordered-subsets maximization expectation approach with 2 iterations and 8 subsets on 128 x 128 matrices and with a 5-mm gaussian post-reconstruction filtering. The 68Ga DOTA-SMS-R PET/CT studies were interpreted by two nuclear medicine physicians having more than 10 years of experience in PET/CT and in determining the somatostatin receptor density in residual tumors or metastatic lesions and to assess treatment response. Images were analyzed visually and semi-quantitatively. Maximum standardized uptake values (SUVmax) were calculated for each single metastatic lesion.

Response measurement

Response measurement was performed according to criteria defined by the European Organization for Research and Treatment of Cancer (EORTC) [22]. There are 4 response definitions based on SUVmax: progressive metabolic disease (> 25% increase in SUVmax or new lesions), stable disease (SUVmax in the target lesions -15% until 25%), partial metabolic response (15%-25% decrease), and complete metabolic response. Additionally, as these tumors are usually indolent in nature, stable metabolic disease - minor response (less than 15% decrease of SUVmax) was also included in the response measurement.

Radiopeptide treatment

The patients received 90Y- or 177Lu-DOTA-TATE (99-100% radiochemical purity as determined by HPLC quality control) by slow intravenous infusion over 20 min. For renal protection the patients received 1,500 ml of an amino acid infusion (Lysine HCL 5% plus 250 ml L-Arginine HCL 10% plus 250 ml NaCl) over 4 hrs. PRRT was performed according to our standard procedure (SOP, Bad Berka PRRT Protocol). Hematological profiles and renal function were periodically examined. The inclusion criteria for performing PRRT were progressive non radiiodine avid/standard treatment refractory DTC/MTC; evidence of adequate SSTR expression on the tumor/metastases (on SR-PET/CT); Hemoglobin ≥ 6 mmol/L, WBC ≥ 4 x 10⁹/L, platelet count ≥ 100 x 10⁹/L; creatinine serum ≤ 110 μmol/L or creatinine clearance ≥ 60 mL/min, Karnofsky Index ≥ 50; average life expectancy > 6 months.
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Figure 2. 77-year-old patient with medullary thyroid carcinoma of the thyroid, pT2 pN1 cMo s.p. thyroidectomy, resection of the left supraclavicular node and a re-cervicectomy and sternotomy for resection of a suspected residual cervical and mediastinal disease respectively, with a total administered activity 11.1 GBq. There was a partial remission of disease after the 3 cycles. A: Shows $^{68}$Ga-DOTA-NOC PET/CT before and after therapy, showing a significant fall of uptake in the somatostatin-receptor positive cervical and mediastinal lymph node metastases. B: Shows the $^{177}$Lu-DOTA-NOC whole body scan (in the middle, and the MIP images of the neck and upper thorax pre- and post-therapy respectively on either side) in anterior view 20 h p.i. after the 3rd PRRT cycle, demonstrating uptake in these metastases eventually leading to the response.

Glomerular filtration rate (GFR) was determined by using Tc-99 m DTPA (and in addition plasma clearance methods) and tubular extraction rate (TER) was measured using $^{99}$Tc-MAG3 in all patients before and serially after PRRT.

**Statistical analysis**

Discrete variables are summarized by counts (percentages) and continuous variables by their median (range), unless stated otherwise. Probabilities of overall survival (mean and median OS) after diagnosis of thyroid carcinoma, and from the time of the first PRRT cycle as well as progression free survival (PFS) were estimated from Kaplan–Meier life tables. The time between the date of first diagnosis or first PRRT and the date of either death or last visit, was used as the ‘time’ variable. Patients treated with 2 or more (maximum 5) cycles of PRRT and had at least two $^{68}$Ga DOTA-SMS-R PET/CTs for restaging were included in progression free survival. All P values are two-sided and P < 0.05 was considered to be statistically significant. Data analysis was performed using the SPSS statistical software package version 17.0 (SPSS Inc., Chicago, USA).

**Results**

There were 16 non-radioiodine-avid and radioiodine therapy refractory thyroid cancer patients (median age at 1st PRRT was 63 years, range: 26-77; male 7, female 9) treated between September 2004 and October 2010 with PRRT in our center using $^{90}$Y/$^{177}$Lu-DOTA-TATE. All patients had undergone total/sub-total thyroidectomy, multiple radioiodine therapies (DTC), repeated surgeries, external beam radiation therapy, chemotherapy, redifferentiation using Roaccutan, and/or laser-induced thermotherapy and exhibiting progressive lymph node, lung, liver and/or bone metastases (Table 1).

Of the 16 patients, 5 patients (1 MTC, 2 FTC, 1 HTC, 1 mixed type) died. The one MTC patient died one year after the second therapy (the tumor status after the 2nd PRRT was unknown). One of the FTC died after having 1 cycle PRRT and also without having any restaging follow-up. The other FTC patient, the HCC patient as well as the patient with mixed type of thyroid cancer died due to the progressive disease after 4th cycle of PRRT. All the patients had metastasis to the lymph nodes, 9 patients had lung metastases, 8 patients had liver metastases, and 7 patients had bone metastases. Of the dead patients, 4 of them had lung metastases and 3 had bone metastases. Kaplan-Meier analysis showed the mean survival after the first PRRT of 4.2 years (95% CI, range 2.9-5.5) and mean of overall survival was 18.43 (95% CI: 13.18-23.86) years (Figure 1).

Response assessment was performed in 11 patients treated with 2 or more (maximum 5) cycles of PRRT. The remaining 5 patients were excluded because they had either only 1 cycle of PRRT (n = 4), or were lost to follow up after the second PRRT (n = 1). The response assessment at the last follow up showed disease stabilization in 4 (36.4%) patients, 2 patients (18.2%) showed partial remission (Figures 2 and 3), and in the remaining 5 patients (45.5%) disease remained progressive. Kaplan-Meier analysis revealed a median progression free survival of 25 (inter-quartiles: 12-43) months (Figure 4). Stable disease was observed in 7 patients after the first course of PRRT and in two patients after 2 courses of PRRT. Of note, stable disease was also observed in 1 of 3 patients having only 1 PRRT (excluded from progression free survival analysis).

The mean age at diagnosis of patients showing good response (stable disease and partial remission) was 52.8 ± 17.7 years old, while non-responding patients (progressive disease)
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were 50.0 ± 13.8 years old (p value = 0.7). The duration between first diagnosis and first PRRT for patients responding well to PRRT was 9.5 ± 8.2 years, not significantly different (p value = 0.9) with non-responders (9.8 ± 5.5 years). Of the 6 patients showing good response. Both FCC patients, 1 MTC, 1 HCC, and the mixed-type patient did not show any response to treatment. Patients with good response
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Figure 4. Kaplan-Meier analysis: median progression free survival in 7 patients after first course of PRRT was 25 months (inter-quartiles: 12-43); in 2 patients stable disease was observed after 2 courses of PRRT.

had less treatment modalities before PRRT than non-responders. Four of them (MTC patients) only had one other treatment option (3 with neck dissection, 1 with external radiation) besides total thyroidectomy, while the other 2 (HTC patients) had 3 and 4 other treatment modalities before.

Four (2 FCC, 1 HCC, 1 mixed type) of 5 non-responders had undergone 3 or more different kind of treatments after the first surgery; the other patient (MTC) only had neck dissection. All the patients had lymph node metastases. Three of the 5 non-responding patients had lung metastases, 2 patients had liver metastases, and 1 patient had bone metastases.

Tumor marker analysis

In the follicular/Hürthle cell group, the human thyroglobulin (Tg) level in serum significantly increased if the disease became progressive. In case of stable and partial remission, however, the Tg course was not predictable (Figure 5).

In MTC patients, calcitonin levels showed a better correlation with the disease status than CEA in serum. In patients with partial remission, calcitonin levels decreased; while calcitonin increased in patients with progression. CEA levels were elevated in all MTC, but did not correlate with the disease status (Figure 6).

In mixed tumors (follicular Hürthle cell and MTC), thyroglobulin levels did not correlate very well with the treatment response, but significantly increased when the disease became progressive. In contrary, calcitonin showed a good correlation with tumor response in the MTC group (Figure 7).

Toxicity

In 16 patients, receiving 45 PRRT courses, minor hematological toxicity was observed in 8 courses. Leukopenia (WHO grade I) was observed in 1 patient after 1 course of PRRT, erythrocytopenia in 2 patients (3 courses), decrease in hemoglobin (WHO grade I) in 2 patients (3 courses), and decrease in both erythrocyte and hemoglobin in 1 patient after 1 course. None of the patients experienced thrombocytopenia.

A change in liver enzymes was observed in 6 patients (in 10 courses of PRRT). An increase of alanine transaminase (ALT) occurred in 2 patients (3 courses, WHO grade 1 in 2 courses and grade 2 in 1 course), however, returned to normal within several days. Mild aspartate transaminase (AST) elevation (grade 1) was observed in 2 patients. Elevated gamma glutamyl transpeptidase (GGT) was observed in 4 patients (in one case considered as grade 3, however, decreased after several days). Only 1 patient had a mild increase (grade 1) of the alkaline phosphatase.

Mild kidney toxicity was observed in 4 patients of total 8 cycles, e.g. slight increase of BUN value (grade 1). One patient presented with elevated serum creatinine (180 μmol/l) which further increased in the following 2 months (300 μmol/l, grade 2). He also had a decreased tubular extraction rate (TER) of 117 ml/min/1.73 (58% of age adjusted normal value), but a normal glomerular filtration rate (GFR) of 76% before the last PRRT. The change in serum creatinine was not considered related to PRRT, since this patient had other pre-existing factors (history of renal obstruction).

Discussion

The best treatment for most patients with differentiated thyroid carcinoma is near-total thyroidectomy followed by ¹³¹I ablation of the thyroid remnant, which reduces the recurrence rate, improves survival and facilitates follow-up. A long delay in initiating this therapy has an adverse and independent effect on prognosis,
more than doubling the 30-year cancer mortality rate [1, 23]. However, in patients with progressive metastatic (or recurrent) differentiated thyroid carcinoma that either do not take up radiiodine or are unresponsive to continued radiiodine therapy, treatment options are limited [1, 8]. Hürthle cell carcinoma (HCC) has poor radiiodine uptake capability (however, synthesizes human thyroglobulin) which is the reason why radiiodine therapy is not effective in HCC [5, 24]. Total thyroideectomy is usually performed to optimize local control and cure, but adjuvant therapy is not effective [25].

Medullary thyroid carcinoma (MTC) represents about 3-16% of thyroid cancer. Although primary surgery is curative in the vast majority of patients treated at an early stage, disease can persist or recur with deleterious effects on quality of life. Local and distant metastases can occur and are the major causes of mortality. Reoperation, embolization, and perhaps radiotherapy can improve the outcome for some patients who are not cured by primary surgery, but there is a need for novel treatments [26]. Survival rate for MTC is not as good as for differentiated thyroid cancer. The overall survival rates for individuals with MTC are 80% for 5 years and 60% for 10 years. Distant metastases are present in 13% of patients at initial diagnosis and portend a poor prognosis, with a 10-year survival rate of only 40% [27].
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The presence of a large and expanding group of somatostatin analogs with different affinities and specificities for the five SSTR subtypes suggests the possibility of targeting antiproliferative therapies with SST agents based upon the expression of distinct subtypes of SSTRs [8, 12]. There is a tendency for less differentiated carcinomas to express a greater variety of SSTR subtypes (12). Another relatively new study also states that somatostatin receptor subtypes are frequently expressed in pathologically altered thyrocytes in contrast to normal thyroid follicular epithelium [28]. These findings support the concept that peptide receptor radionuclide therapy could be a promising novel therapeutic modality.

Somatostatin receptor type 5 (SST5) and type 1 (SST1) are the most frequently and consistently expressed SST receptors in thyroid carcinoma; hence the most appropriate targets for subtype-specific somatostatin analogs. The lack of expression of SST2 mRNA in most thyroid carcinoma cells suggested that SST2-specific analogs would have little therapeutic activity [12]. However, another study using northern blot analysis showing regular expression of somatostatin receptor type 1 (SST1), type 3 (SST3), type 4 (SST4) and type 5 (SST5) in all types of thyroid carcinoma. Somatostatin receptor type 2 (SST2) was expressed with moderate intensity in most of MTC, but not in any papillary or follicular thyroid cancer, and irregularly expressed in Hürthle cell adenoma and Hürthle cell carcinoma [15]. This might explain the relatively poor response of FTC and HCC compared to MTC, since the radiopharmaceutical used was $^{177}$Lu/$^{90}$Y-DOTA-TATE, which specifically targets SST2. In future, other somatostatin analogs targeting different types of somatostatin receptors that are more heavily expressed in each type of thyroid cancer might be more effective.

Patients with good response had less treatment modalities before PRRT than non-responders. The therapeutic effect of ionizing radiation and many cytotoxic drugs is caused by double-strand breaks in DNA [29]. Radiation also induces a wide range of other effects, including numerous base alterations, single-strand breaks and other modifications of the DNA double helix, which are in general repaired by the cell [30]. On the other hand, unrepaired or mis-repaired double-strand breaks leads to cell death or a surviving cell with an altered genome [31], which may be responsible for dedifferentiation of somatostatin receptors in patients who previously had external radiotherapy and/or chemotherapy.

Nayak et al. suggest that gemcitabine pretreatment up-regulates SSTR expression and acts as a radiosensitizer and could potentially increase the therapeutic effects of PRRT [32]. In the present study, all patients came to our department after being unresponsive to other treatments, so PRRT was not designed to be combined with other therapies, but rather the last treatment option. Based on our experience, we suggest that PRRT should be considered earlier in the course of disease, either alone or in combination with other treatment modalities; particularly radiosensitizing chemotherapy may contribute to a higher success rate [33, 34].

It seems that lung metastasis is a poor prognostic factor. Of 9 patients with lung metastases, 4 patients demonstrated progression under PRRT, two patients had stable disease, and one partial remission, while the status of the rest was not known.

In the follicular/Hürthle cell group, increase of serum Tg was indicative for progression, prov-
ing that the tumor cells still have the capability to produce Tg, although lesser than well-differentiated iodine-avid cancers do. This might be related to DNA methylation. As compared with normal cells, the malignant cells show major disruptions in their DNA methylation patterns [35]. Methylation happens to thyroid-specific genes, such as those for sodium/iodide symporter (NIS) [36] and thyroglobulin [37]. Pichonet et al found that reporter-gene expression from a plasmid containing only the proximal thyroglobulin gene promoter is sensitive to DNA methylation even in fully differentiated thyrocytes. Transcription from methylated plasmids containing the thyroglobulin gene enhancer and proximal promoter is also clearly reduced when the transfected cells are maintained under less-differentiated conditions. DNA methylation does not constitute a prerequisite for thyroglobulin gene expression in differentiated thyrocytes, where the thyroglobulin gene enhancer and promoter are activated. However, the production of thyroglobulin transcripts could be severely impaired when this activation is not maximal, as in the case of less-differentiated cells [37]. It can be assumed that in our patients’ cells were in the process of dedifferentiation, because all patients had undergone radioiodine ablation and/or external beam radiation therapy and/or chemotherapy. It might be postulated that if well-differentiated iodine-avid thyroid cancer is the candidate for ¹³¹I therapy, the candidate for PRRT is the non-iodine-avid thyroid cancer with differentiated thyroid cells, albeit to a lesser degree and expressing strongly SST receptors.

In MTC, calcitonin is a well-established sensitive and specific biomarker and used in follow up for detecting recurrence and to assess response to therapy, even in occult disease [38]. Serum CEA may be a better predictor of tumor aggressiveness. Expression of CEA in MTC is considered as a marker of dedifferentiation and associated with more aggressive forms of MTC [39]. A study by Behr et al. states that higher CEA expression seems to be associated with more aggressive forms of MTC [40].

The frequent low dose therapy performed in our patients is based on the concept of delivering therapeutic radiation in multiple small-dose fractions rather than as a large single exposure for maximizing a differential between responses of dose limiting normal tissues and the tumor [41]. By using this fractionated regimen, no serious adverse effects were observed, and only mild, reversible hematological toxicity occurred despite the heavy pretreatment of the patients. Fractionated regimens given were also considered to reduce renal toxicity [42]. By administering positively charged amino acids, which have been proven to be useful in reducing the uptake of the radiolabeled peptides to the kidney [43], no significant kidney toxicity occurred.

Our study has some limitations. First, there were three peptides (TOC = 1, NOC = 1 and TATE = 14) used for primary staging and response assessment, which may lead to slight SUVmax variation from peptide to peptide. However, we used the same peptide and protocol for each patient from the first evaluation to the last follow-up and only two patients were studied with peptides other than TATE. In addition, some studies also confirmed that ⁶⁸Ga DOTA-TATE and ⁶⁸Ga DOTA-TOC had a comparable diagnostic value [44], as well as between ⁶⁸Ga DOTA-TATE and ⁶⁸Ga DOTA-NOC [45]. In a study comparing this three peptides (labeled with ¹⁷⁷Lu), it was found that no significant differences in tumor kinetics and mean absorbed tumor dose [46]. Second, although these preliminary results are promising, only 16 subjects were studied, and therefore, further prospective studies with a larger sample size will be necessary to validate these findings and establish the role of PRRT and ⁶⁸Ga DOTA-Somatostatin Receptor (SMS-R) PET/CT as important elements of care in this population.

Conclusion

In non-radioiodine-avid or radioiodine therapy refractory thyroid cancer patients, PRRT is a promising therapeutic option with minimal toxicity, promising response rates and significant survival benefits. MTC had a comparatively better response for PRRT than non-radioiodine-avid DTC or mixed-type patients.

These findings need to be confirmed in further studies with a larger patient population and probably using other radiopeptides with higher affinity to the predominantly expressed sstr subtypes in thyroid cancer. PRRT should be considered earlier in the course of progression
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(in combination with other treatment options) and not as the modality of last resort.

Disclosure of conflict of interest

None.

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