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Peptide Receptor Radionuclide Therapy (PRRT) of Medullary and Nonmedullary Thyroid Cancer Using Radiolabeled Somatostatin Analogues

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As therapeutic options in advanced medullary and non–iodine avid differentiated (nonmedullary) thyroid cancers are limited and associated with significant toxicity, targeting of somatostatin receptors (SSTRs) for internal radiation therapy provides a promising option. Theranostics (therapy and diagnosis) using radiolabeled somatostatin analogues has proved to be a milestone in the management of SSTR-expressing tumors. Peptide receptor radionuclide therapy using ^{177}Lu-labeled or ^{90}Y-labeled somatostatin analogues may have a significant role in the management of medullary and nonmedullary thyroid cancers in those patients where PET/CT with ^{68}Ga-labeled somatostatin analogues demonstrates significant SSTR expression.

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Introduction

Thyroid cancer (TC) is the most common endocrine malignancy. In recent decades, the diagnosis of TC has been increasing worldwide. The incidence rate in the US increased by 4.4% per year from 2007-2011.[1]

Differentiated TC (DTC) that includes papillary TC (PTC), follicular TC (FTC), Hurthle cell TC (HCTC), or follicular carcinoma-oxyphilic type is curable and has a relatively good prognosis with 10-year survival rate of 85%-99%.[2,3] The standard treatment of DTC involves total or near-total thyroidectomy followed by ablation of remnant thyroid tissue by radioiodine treatment. Tumor recurrences occur in approximately 20% of DTCs. Radioactive iodine is used for the detection (^{123}I and ^{131}I) and treatment (^{131}I) of recurrent DTC, however, 20%-30% of PTCs and FTCs with recurrent or persistent disease and most of the HCTC tumors do not accumulate radioiodine because of the mutation of the natrium-iodide symporter gene (4%-6% of patients diagnosed with DTC).[4] Medullary TC (MTC) is another subtype of TC, which develops from parafollicular C cells of thyroid gland, of neural crest origin. It accounts for almost 5% of all TCs.[5] Because C cells do not express natrium-iodide symporter gene, MTC does not take up radioactive iodine and its management is more difficult than DTC with a worse prognosis. The therapeutic and diagnostic options for non–iodine avid DTC and MTC are limited. Chemotherapy, external beam radiation therapy, biological agents such as RET and MEK inhibitors, and surgery have not demonstrated promising clinical outcomes.[6-8]

In the 1990s, some studies demonstrated the involvement of somatostatin receptors (SSTRs) in the regulation and proliferation of normal thyroid cell and tumor tissue. Following these findings, several investigators used different radiolabeled somatostatin analogues for diagnosis and treatment of MTC and non–radioiodine avid DTC.[9-18]

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Molecular Basis

Somatostatin is a cyclic peptide hormone with a short plasma halflife (1-3 minute). It has two bioactive forms, with 14 and 28 amino acids, which are produced by alternative cleavage of a single proprotein. Its primary action is to regulate the endocrine system, modulation of neurotransmission, and cell proliferation through interaction with membrane G–protein coupled SSTRs. SSTRs are normally expressed in different organs such as thyroid, hypophysis, adrenal glands, uncinate process of the pancreas, kidneys, spleen (activated lymphocytes), and in the gastrointestinal tract in different quantities. Five different subtypes of SSTR have been described in humans (SSTR 1-5), SSTR 2 has two isoforms, SSTR 2A and SSTR 2B.[19,20] Following the successful application of ^{111}In-diethylenetriaminepentaacetic acid (DTPA)-D-Phe1-octreotide (^{111}In-pentetreotide [OctreoScan, Mallinckrodt, Inc, St Louis, MO]) as the first radiolabeled somatostatin analogue for diagnosis and staging of primary and metastatic neuroendocrine tumors (NETs) in early 1990s, therapeutic and diagnostic approaches using radiolabeled somatostatin analogues have been introduced for different receptor positive malignancies.[19-22] Currently, radionuclide therapy is an accepted treatment modality for metastatic well-differentiated NETs.[23-25] The rationale of using peptide receptor imaging and peptide receptor radionuclide therapy (PRRT) for tumors with neuroendocrine or endocrine origins is the overexpression of different subtypes of SSTR on these tumor cells. The mechanism of antitumor effect of PRRT has been explained based on receptor-mediated internalization and intracellular retention of the radiopeptide. As a result, PRRT is able to deliver a high dose of radiation to intracellular components of the cancer cells, which results in tumor shrinkage or even cure.[19,20] Another potential target for radiolabeled somatostatin analogues is upregulated SSTR 2 in the peritumoral vessels which causes an antiangiogenic response during radionuclide therapy.[26] It is worth mentioning that the advantages of small peptides (eg, somatostatin analogues, cholecystokinin, and exendin-3) over antibodies for targeted therapy are better pharmacokinetic characteristics and very low antigenicity, which makes them nearly ideal ligands for receptor-based radionuclide imaging or therapy.

Several studies demonstrated expression of five SSTR subtypes in human thyroid carcinoma including nonmedullary and medullary tissues.[27-29] They reported conflicting results for SSTR subtype expression on different thyroid tumor cells (Table 1). These discrepant findings may stem from methodological differences, such as types of tissue analyzed (TC cell lines vs human thyroid tumor samples) and techniques for analysis (immunohistochemistry vs messenger RNA analysis through northern blotting or reverse transcription-polymerase chain reaction).

Cold Somatostatin Analogues

Although cold somatostatin analogues have been shown to be helpful in symptomatic and biochemical improvement in patients with NET, preclinical and clinical studies showed contradictory results on the antitumor effects of these compounds for NETs as well as TCs.[37,38] Kohlfuerst et al injected long-acting octreotide once per month intramuscularly over a

Table 1 Somatostatin Receptor Expression on Different Types of Thyroid Cancer Cell

Study	Evaluated Thyroid Tumors Subtypes	Methods	Conclusion
Pisarek et al[28]	27 (14 PTC, 4 ATC, and 11 benign)	IHC	SSTR 1 and SSTR 5 are most frequently (71.4%) expressed in PTC and ATC; SSTR 2A in less than 40%.
Pazaitou-Panayiotou et al[27]	47 (38 PTCs, 4 FTCs, 2 ATCs, and 3 HCTCs)	IHC	SSTR subtype expression in normal thyroid tissue was low or absent. SSTR 2 and 3 were expressed in all nonmedullary thyroid carcinomas, SSTR 1 and 5 in 75% and SSTR 4 in 38%
Mussig et al[30]	93 (67 PTCs and 26 FTCs)	IHC	SSTR 1-5 were detected in 15%-30% of thyroid tumors.
Sancak et al[31]	17 PTCs	IHC for SSTR 2	SSTR subtype 2 was expressed in PTCs
Klagge et al[32]	45 (20 PTCs, 20 FTCs, and 5 ACs)	mRNA expression for SSTRs	Predominant expression of SSTR 2 and SSTR 5, weak expression of SSTR 1 and SSTR 3
Pisarek et al[33]	Four malignant surgical samples and five benign surgical samples	IHC and RT-PCR and correlated findings	Expression of SSTR 1, SSTR 2A, and SSTR 2B in malignant tissue may be on the cell membrane or cytoplasmic, whereas in noncancer tissue the expression of these receptors was only cytoplasmic
Druckenthaner et al[34]	17	IHC and RT-PCR and correlated findings for SSTR2	Thyroid tumors expressed SSTR 2 and less predominantly SSTR 3 and 5.
Forssell-Aronsson et al[35]	Nine PTCs and two HCTCs	mRNA expression northern-blot analyses	All thyroid tumors regularly expressed SSTR 1, 3, 4, and 5. SSTR 2 was not detected in PTCs and was irregularly expressed in HCTCs.
Ain et al[36]	Eight cell lines (two PTCs, two FTCs, and four ATCs)	mRNA expression in thyroid cancer cell lines	Predominant expression of SSTR 3 and SSTR 5 on monolayers of thyroid cancer cell lines

IHC, immunohisto chemistry; mRNA, messenger RNA; RT-PCR, reverse transcription-polymerase chain reaction.

period of 6 months to treat eight patients with progressive radioiodine-negative but SSTR positive TC (1 PTC, 4 FTC, and 3 anaplastic TC [ATC]). All patients showed progressive disease during the treatment.[38] Zlock et al treated six patients (4 PTC or FTC, 1 HCTC, and 1 MTC) with subcutaneous daily long-term octreotide for up to 12 months. All biochemical and imaging-based biomarkers indicated progressive disease during treatment.[39] On the contrary, Robbins et al treated two PTC patients (one with radioiodine avid lesions, one having no ^{131}I uptake) with 3-4-month course of long-acting octreotide. They observed decreasing tumor volume and SUVs on follow-up FDG PET/CT in both the patients. In addition, some in vitro studies showed antitumor effect on carcinoma cell lines whereas they were not able to demonstrate any antitumor effects of cold somatostatin analogues in animal experiments of TC.[40,41] In short, most of the studies questioned the value of cold somatostatin analogues as an antitumoral agent for thyroid carcinomas.

Radiolabeled Somatostatin Analogues

A radiolabeled somatostatin analogue generally consists of the following three main parts: a synthetic analogue of somatostatin (cyclic octapeptide) such as octreotide or Tyr3-octreotate or Tyr3-octreotide, a chelator such as DTPA or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), and a radioactive component. Radionuclides commonly used for PRRT of TCs are ^{177}Lu and ^{90}Y.

Owing to the short half-life of endogenous somatostatin, its several synthetic analogues with different affinity for certain types of SSTRs have been developed for diagnostic and therapeutic use in tumors expressing SSTRs. Table 2 summarizes the use of PRRT in DTC. In late 1970s, Bauer et al[42] synthetized octreotide as the first octapeptide somatostatin derivative, which has essential amino acids enabling it to bind to SSTR. Octreotide has a very high affinity for SSTR 2. Primary studies used ^{111}In-DTPA-octreotide for PRRT of TC as well as various endocrine tumors.[43,44] The results of these studies were not very promising. In general, ^{111}In-coupled peptides are not perfect compounds for PRRT because of a poor tissue penetration. Because it is an auger electron-emitting radionuclide and range of the emitted particles (nanometers to micrometers) does not exceed the cell diameter, tangible objective responses were infrequently achieved using ^{111}In for PRRT.[45]

In an effort to find a more effective radiopeptide, DOTA-Tyr3 octreotide (DOTATOC) was developed and labeled with different radionuclides for imaging as well as for therapy. As a consequence of the replacement of phenylalanine by tyrosine as third amino acid in the octretide, this molecule has increased hydrophilicity and affinity for SSTR 2. In addition, DOTA used in this compound as the chelator allows stable binding with ^{90}Y or ^{177}Lu, the two β-emitting radionuclides most commonly used for PRRT. Replacement of the alcohol group at C terminus of the peptide by a carboxylic acid group resulted in the formation of DOTA-Tyr3 octreotate (DOTATATE) that has a six-fold to nine-fold increased affinity for the SSTR 2. Yet, the DOTATATE binding affinity to other SSTRs was less than expected. Binding to SSTR 5 and SSTR 3 was low and to SSTR 1 and SSTR 4, very little. The third generation of somatostatin analogues is DOTA-1-Nal3-octreotide (DOTANOC), in which the third amino acid is 1-naphthylalanine instead of phenylalanine. This compound has been shown to have improved affinity for SSTR 2 and higher affinity to SSTR 3 and SSTR 5, resulting in coverage of a wider spectrum of SSTR (pan-somatostatin characteristics) and improving the diagnosis of NET and various other tumors with atypical expression of SSTR subtypes.[46] However, wide affinity spectrum of DOTA-NOC results in higher in vivo uptake for whole body and normal tissue and consequently the higher potential of bone marrow toxicity.[47] Therefore, some institutions including our center do not recommend using DOTANOC for PRRT of NETs.[48,49]

Newer somatostatin analogues such as DOTANOC-ATE ([DOTA-1Nal3, Thr8]-octreotide) and DOTA-BOC-ATE ([DOTA, BzThi3, Thr8]-octreotide) are in the preclinical stage of development. These "fourth-generation analogues" have been reported to show very high affinity for SSTR 2, SSTR 3, and SSTR 5 and intermediate high affinity for SSTR 4, which possibly make them good candidates for thyroid tumor cell expressing high level of SSTR 3 or 5 despite low expression of SSTR 2.[19,20] Recently, preclinical and clinical studies have shown that radiolabeled SSTR antagonists such as ^{177}Lu-DOTA-JR11 [^{177}Lu-DOTA-Cpa-c(DCys-Aph(Hor)-DAph(Cbm)-Lys-Thr-Cys)-DTyr-NH_2] and ^{177}Lu-DOTA-BASS [^{177}Lu-DOTA-[p-NO_2-Phe-c(DCys-Tyr-DTrp-Lys-Thr-Cys)-DTyr-NH_2] are superior to SSTR agonists for targeting of tumors.[50-53] A possible explanation is they have higher affinity for SSTRs, even though they are not internalized into tumor cells.[52] Although small clinical studies have shown clinical feasibility and favorable tumor-to-organ, tumor-to-kidney or -bone marrow dose ratio of different SSTR antagonists in NET patients and their introduction has been suggested as paradigm changer of PRRT, further systematic studies are warranted before replacing the somatostatin agonists by antagonists in patients with TC.[50,51,54]

Radionuclide Selection

Yttrium-90 and Lutetium-177 are the most frequently used radionuclides in PRRT. They have different physical characteristics, chiefly, different emitted energies, which result in various maximum tissue penetration ranges (12 mm for ^{90}Y vs 3 mm for ^{177}Lu). ^{90}Y has the highest energy of β particles (935 keV) and highest maximum tissue penetration, resulting in "crossfire effect" on nearby tumor cells. Owing to crossfire effect, ^{90}Y β particles can extend more than several cell diameters and are able to irradiate the tumor cells not bound by the radiopharmaceutical. This makes it the desirable radionuclide for large tumors and tumors with poor vascularization. Although the crossfire effect is favorable to overcome receptor expression inhomogeneity along with aforementioned benefits in bulky tumors, the long range of the ^{90}Y β

Table 2 Peptide Receptor Radionuclide Therapy in Patients With DTC

Study	N	Subtypes	Response Assessment Criteria	Radiopharmaceutical	Cumulative Dose (GBq)	Toxicity	Antitumor Outcome Percentage—Disease Control (TTP in Months)
Gorges et al[16]	3	Three HCTC	NA	^{90}Y-DOTATOC	1.7-9.6	NMSE	33%—1 SD (21)
Waldherr et al[67]	7	Three FTC and four PTC	WHO	^{90}Y-DOTATOC	1.7-14.8	1 (Hem III)	29%—2 SD (8.8)
Chinol et al[74]	2	Two PTC	SWOG	^{90}Y-DOTATOC	07.4	NA	NA
Valkema et al[43]	5	One FTC and four PTC	SWOG	^{111}In-DTPA-Octreotide	29.5-83.2 4	NA	20%—1 SD (NA)
Virgolini[75]	25	25 unclassified TC	WHO	^{90}Y-DOTALAN	0.9-7.0	NMSE	56%—3 MR (NA), 11 SD (NA)
Christian et al[11]	1	One HCTC	NA	^{90}Y-DOTATOC	NA	NA	NA
Gabriel et al[76]	5	Three FTC and two PTC	NA	^{90}Y-DOTATOC	5.6-7.6	NA	100%—SD (5)
Stokkel et al[44]	9	Four FTC and five PTC	Radiological or biochemical	^{111}In-DTPA-Octreotide	14.3-33.1 4	NA	44% Radiological—4 SD (NA) 66% Biochemical—6 SD (NA)
Teunissen[77]	5	One FTC, one PTC, and three HCTC	NA	^{177}Lu-DOTATATE	22.4-39.11	NA	80%—PR (22+), 1 MR (43), 2 SD (18,24+)
Budiawan et al[13]	8	Four FTC, three HCTC, and one mixed	EORTC	^{90}Y-DOTATATE or ^{177}Lu-DOTATATE		NMSE	33%—1 PR, 1 SD, 2 NA, 4 PD
Versari et al[72]	11	Four PTC, four FTC, one HCTC, and two insular	EORTC RECIST	^{90}Y-DOTATOC	4.3-17.9	One permanent renal toxicity	60% RECIST 63% PERCIST
Campenni et al[78]	1	one DTC	RECIST Biochemical	^{177}Lu-DOTATOC	7.77	NMSE	100% radiological—SD (5+) 100% biochemical—SD (5+)
Czepczynski et al[17]	11	Five FTC, three PTC, and three HCTC	RECIST Biochemical	^{90}Y-DOTATOC	21.0-53.3	NMSE	27% RECIST 45% Biochemical

EORTC, European Organization for Research and Treatment of Cancer; LAN, lanreotide; NMSE, no major side effect: WHO kidney, hepatic, and hematological toxicity $\geq$ grade III; NA, not available; PERCIST, positron emission tomography response criteria in solid tumors; RECIST, response evaluation criteria in solid tumors; SWOG, Southwest Oncology Group; TATE, -Tyr3 octreotate; TOC, -Tyr3 octreotide; TTP, time to progression; WHO, world health organization.

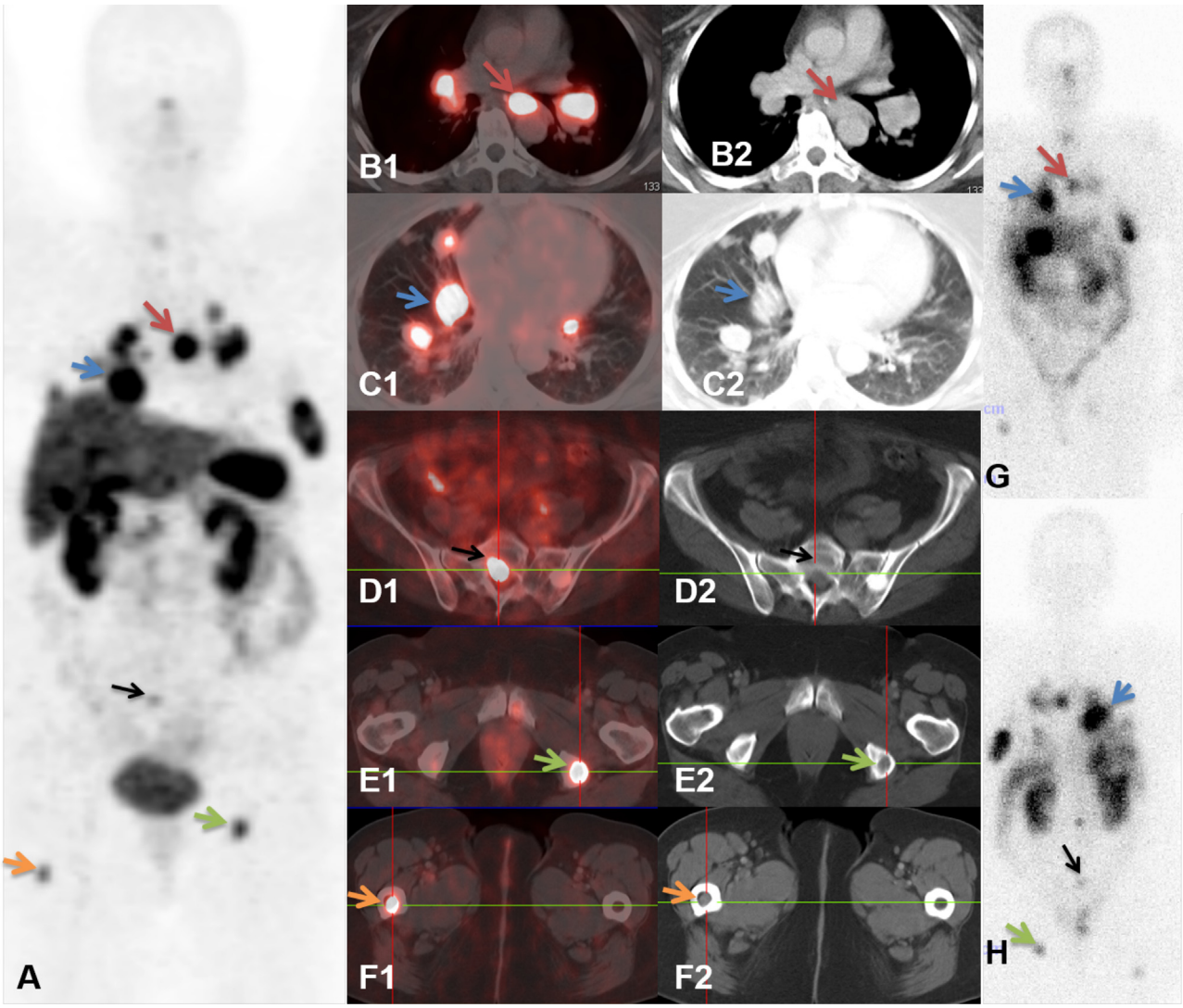

Figure 1 A 43-year-old female with oncocytic follicular carcinoma of the thyroid (initial stage pT4), first diagnosis 10 years back, was referred to our center with progressive lymph node, pulmonary, hepatic, osseous, and cerebral metastases after surgery, external radiation, chemotherapy, and 3 radioiodine therapies. The baseline ^{68}Ga-DOTATOC PET/CT (A-F) revealed intense somatostatin receptor (SSTR) expression in the metastases, which provided a theranostic basis for the administration of peptide receptor radionuclide therapy (PRRT). Intense uptake was demonstrated on PET/CT (A—MIP, B1-F1—PET/CT transverse images, and B2-F2—corresponding CT transverse images) in mediastinal lymph node (B—red arrow), lung (C—blue arrow), sacrum (D—black arrow), left ischium (E—green arrow), and right femur (F—orange arrow) which is also seen on ^{177}Lu-DOTATATE posttherapy whole-body scans (G—in anterior view; and H, in posterior view).

particles appears to increase the possibility of renal toxicity.[20] On the other hand, ^{177}Lu emits intermediate-energy β particles (133 keV), resulting in a maximum tissue penetration range up to 3 mm, which makes it a preferable radionuclide for smaller tumors. In addition to β particles, ^{177}Lu emits two gamma peaks of 113 and 208 keV, which makes it a suitable compound for post-therapeutic gamma camera dosimetry. Another less-studied difference between these radionuclides is their physical halflife (6.7 days for ^{177}Lu vs 2.7 days for ^{90}Y), which may have an effect on their therapeutic (and adverse) effects. These physical characteristics as well as other tumor-related and non–tumor-related factors should be considered to develop an appropriate PRRT protocol for each patient (Fig. 1).[20]

Medullary TC

Survival statistics of MTC demonstrate a 10-year overall survival rate of 75%, however, in cases of advanced or metastatic disease, it drops to 40%.[55,56] In spite of aggressive surgical treatment, almost 50% of patients show residual disease or develop tumor recurrence—common sites of metastatic involvement in MTC are cervical nodes, lung, liver, and bones.[57] Reoperation is the commonly followed treatment option for neck recurrence, either with or without radiotherapy, depending on the extent of involvement. However, there is seldom a significant decrease noted in calcitonin levels in these patients, and hence, distant metastases are quite frequent.[56] In the scenario of distant metastases, the aim of

treatment is to reduce the symptoms and to improve the quality of life. Conventional chemotherapy has limited efficacy and considerable toxicity in patients with advanced MTC and is therefore not recommended.[58] Better understanding of tumor biology, especially about the RET proto-oncogene, which encodes a receptor tyrosine kinase, has led to the development of newer targeted agents such as vandetanib and cabozatinib.[59] MTCs are known to express SSTR 2 that facilitates imaging with ^{99m}Tc-labeled and especially ^{68}Ga-labeled analogues.[29] Hence, tracer concentration at disease sites confirms SSTR expression that is the premise for therapy with similar peptides bound to therapeutic radioisotopes like ^{177}Lu or ^{90}Y.[19,20]

In vitro data have shown that MTC cells not only produce somatostatin but also express corresponding receptor analogues.[60,61] SSTR type 2 (SSTR 2) is expressed with moderate density in most MTCs. However, probably because of the low density of SSTR 2, only approximately 50%-70% of MTCs can be visualized with scintigraphy using ^{111}In-labeled octreotide, which also lacks in resolution.[62,63] This makes pretherapeutic ^{68}Ga-labeled peptide PET/CT imaging mandatory for confirmation of SSTR expression.

Octreotide administered short or long term in symptomatic MTC results in improvement of neuroendocrine symptoms, especially in diarrhea and flushing, however, reports of objective tumor response are anecdotal.[64] As a combination of human recombinant α-interferon and octreotide increased response rate in metastatic carcinoid, the same combination has been tested in MTC. There was no objective response recorded and only symptomatic benefit was achieved in some patients.[65,66] In conclusion, studies so far have excluded significant antiproliferative activity of cold octreotide in patients with advanced MTC. Yet, the poor results of therapy with cold somatostatin analogues should not exclude good response to therapy with radiolabeled peptides. Cold somatostatin analogues exert their therapeutic role by direct inhibition of variety of signal transduction pathways in cancer cells or indirectly through suppression of the secretion of growth-promoting hormones. In radiopeptide therapy, the main goal is to deliver a high radiation dose to tumors expressing SSTR 2 although sparing receptor-negative, normal tissues. PET/CT imaging with ^{68}Ga-peptides (DOTATOC or DOTANOC or DOTATATE) to confirm SSTR expression is a necessary prerequisite for PRRT in MTC. SSTR imaging also provides information about the disease burden in the form of tracer avid sites. Based on the intensity and distribution of tracer, further therapy can be planned using therapeutic radionuclides like ^{177}Lu or ^{90}Y.

In a pilot study, Waldherr et al[67] in 2001 reported the first series of 28 patients with TC including 12 MTC, 4 PTC, 3 FTC, and 1 ATC treated with ^{90}Y-DOTATOC. All patients had ^{111}In-DOTATOC or octreoscan positive progressive disease before PRRT. They received a total dose of 1700-7400 MBq/m^2, in one to four injections at intervals of 6 weeks. However, the overall antitumour outcome (objective response and stable disease) was 35%, 42% in MTC, 29% in DTC, and 0% in ATC, the objective complete or partial response (PR) rate was 0%. A stable disease was achieved in 35% (7 of 20), and remaining 65% (13 of 20) had progressive disease. The median time to progression of stable disease patients was 8 months (range: 3-14 months). No grade III or IV hematological or renal toxicities were observed.

In 2004, Bodei et al[18] published a series comprising 21 patients (8 women and 13 men) with histologically proven diagnosis of MTC. All patients had nonresectable locoregional disease or distant metastases and were treated with ^{90}Y-DOTATOC. The overall antitumor response (objective response plus stable disease) was 67%, however complete response was documented only in two (10%) patients and no partial or minor response was observed. Seven (33%) patients did not respond to the therapy and continued to progress. The duration of overall response (complete remission plus stable disease) ranged from 3-40 months. In one (5%) patient ^{90}Y-DOTATOC therapy resulted in normalization of serum calcitonin and carcinoembryonic antigen levels and the other five (24%) patients responded with biochemical partial remission. Stabilization or increase in serum markers was observed respectively in 3 (14%) and 12 (57%) patients. There was no reported toxicity in any of the treated patients. Patients with smaller tumors responded better, suggesting that PRRT should be started in earlier phases of the disease.

In a phase II trial, Iten et al[15] investigated the response, survival, and long-term safety profile in 31 patients of metastasized MTC, treated with ^{90}Y-DOTATOC. Median survival was 91 months from the time of diagnosis and 15.7 months from the time of first treatment. Responders had a significantly longer survival compared with nonresponders (108.8 vs 80.4 months).

In a recent study by Vaisman et al,[68] 16 patients with progressive MTC were evaluated by ^{111}In DTPA-octreotide scintigraphy. Seven patients demonstrated high ^{111}In-DTPA-octreotide uptake and were treated with four cycles of 200 mCi ^{177}Lu-DOTATATE with 6-10-week intervals between cycles. Response to treatment was evaluated using CT scans more than 8-12 months after the fourth cycle of PRRT and concurrently they evaluated quality of life of patients using SF-36 questionnaires. Three patients were classified as having PR, three patients had stable disease and one patient had a progressive disease. All responders (six patients) reported improvement in quality of life and cancer-related pain. There were no grade III or IV hematological or renal toxicities. Makis et al reported two cases of metastatic MTC, who were treated with four doses of ^{177}Lu-DOTATATE with 2-month intervals between cycles. Both achieved stable disease for 10 and 8 months, respectively, based on ^{111}In-octreotide scan imaging.[69]

We studied a consecutive cohort of 28 patients (14 men, 14 women, mean age of 47.9 years, age range: 26-72 years) between 2004 and 2012 with histopathologically proven recurrent medullary TC and widespread distant metastases (unpublished data). All patients had undergone primary surgery, conventional chemotherapy, or radiotherapy treatment regimes, depending on the stage at presentation. In addition, the patients had received site-specific treatments. SSTR expression was confirmed on ^{68}Ga-DOTATOC PET/CT. Patients were treated with PRRT (up to five times) at our center

using ^{90}Y or ^{177}Lu-DOTATATE. Primary end point was treatment response assessed on follow-up ^{68}Ga-DOTATOC PET/CT, with survival statistics being the secondary end point. Comprehensive relevant clinical information were gathered from the referred medical profiles and during follow-up periods (until death) at our institute. Based on European Organization for Research and Treatment of Cancer criteria, 17 of 28 (60.7%) patients showed stable disease, 5 of 28 (17.7%) showed PR, whereas 6 of 28 (21.4%) showed disease progression.[70,71] Thus, 22 of 28 patients had nonprogressive disease, a significant change in outcome considering the baseline pre-PRRT disease status (Fig. 2). The median survival in patients with SD was 36 months and with PR was 72 months. The median survival for patients with progressive disease was 24 months. Overall, the survival statistics from the available literature are encouraging. With very low incidence of toxicity, this therapeutic option also provides a good quality of life.

Differentiated Non–Iodine Avid TC

In mid 1990s several studies showed the diagnostic value of SSTR scintigraphy in patients with non–radioiodine avid DTC; however, the first study using PRRT in these patients was published in 2001. In a small study, Gorges et al[16] reported the dosimetry and clinical data of ^{90}Y-DOTATOC therapy in three patients with progressive DTC (up to 9.3 GBq per four cycles). They concluded that PRRT appeared to be ineffective owing to disease progression; however, only one of their patients received four cycles of PRRT and two other patients were treated only with one and two cycles, respectively. On the other hand, well-designed recent studies showed promising results. Versari et al[72] in a prospective study treated 11 radioiodine-negative patients with DTC with two to six cycles of ^{90}Y-DOTATOC and assessed treatment response using

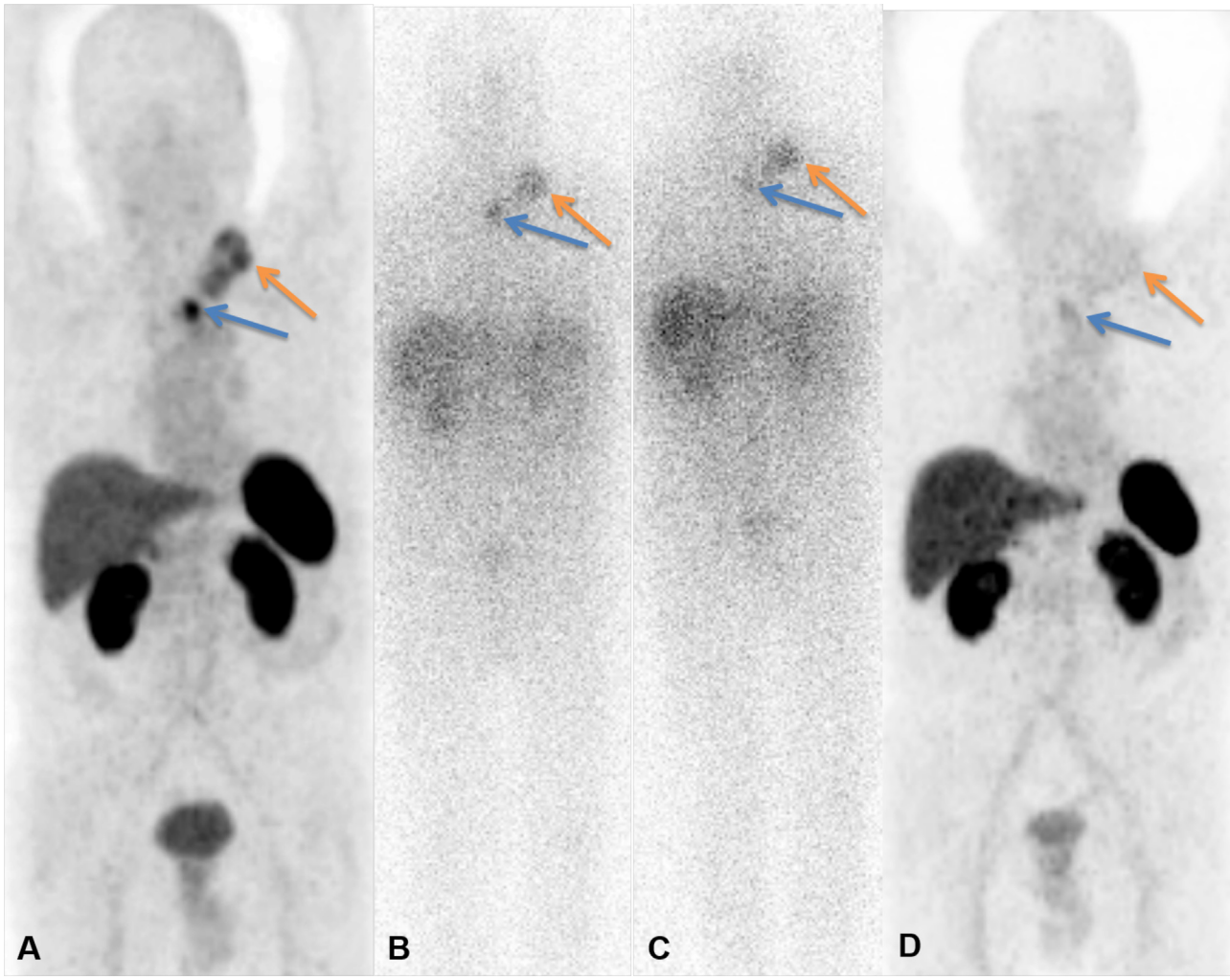

Figure 2 A 76-year-old male with recurrent sporadic medullary thyroid carcinoma involving the left lobe with infiltration of trachea and esophagus as well as supraclavicular and mediastinal lymph node metastases, s.p. complete thyroidectomy, recervicotomy, and sternotomy to operate the recurrence. The baseline ^{68}Ga-DOTANOC PET/CT demonstrated significant SSTR expression (A) in the extensive left supraclavicular lymph node mass (orange arrow) and the retrotracheal lymph node (blue arrow). The patient was treated with two cycles of PRRT using ^{90}Y-DOTATATE. The posttherapy whole-body Bremsstrahlung scans (B—first cycle, C—second cycle) demonstrated corresponding high uptake at the two sites. The follow-up ^{68}Ga-DOTANOC PET/CT (D) revealed partial remission of the disease after two cycles of PRRT.

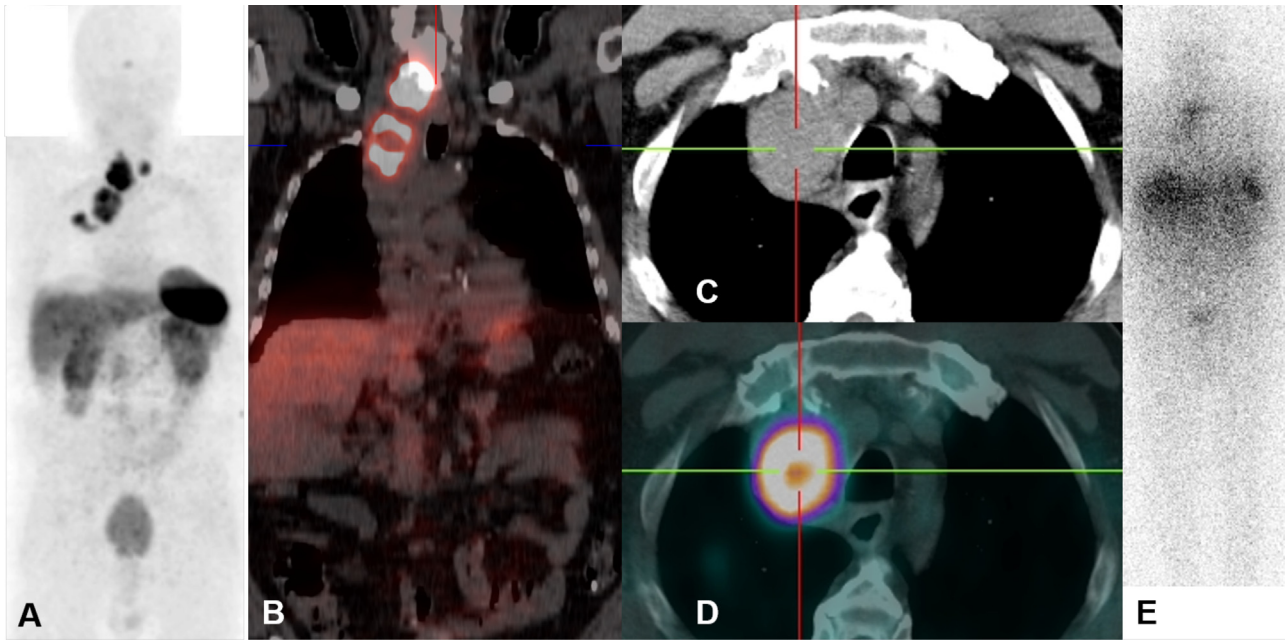

Figure 3 A 65-year-old male with follicular thyroid carcinoma—local recurrent disease with left supraclavicular and large mediastinal lymph node metastasis as well as pulmonary metastasis. The baseline ^{68}Ga-DOTATOC PET/CT (A-D) demonstrated tracer uptake at these sites, also seen on the ^{90}Y-DOTATOC whole-body scan after the first PRRT cycle (E).

serial ^{68}Ga-DOTATOC PET/CT scans. In patient-based analysis, PRRT induced disease control (SD and PR) was achieved in 60% and 63% of patients according to response evaluation criteria in solid tumors and European Organization for Research and Treatment of Cancer criteria, respectively. In lesion-based analysis, they reported 71% disease control based on Response Evaluation Criteria In Solid Tumors criteria for nonosseous metastases. They used strict inclusion criteria

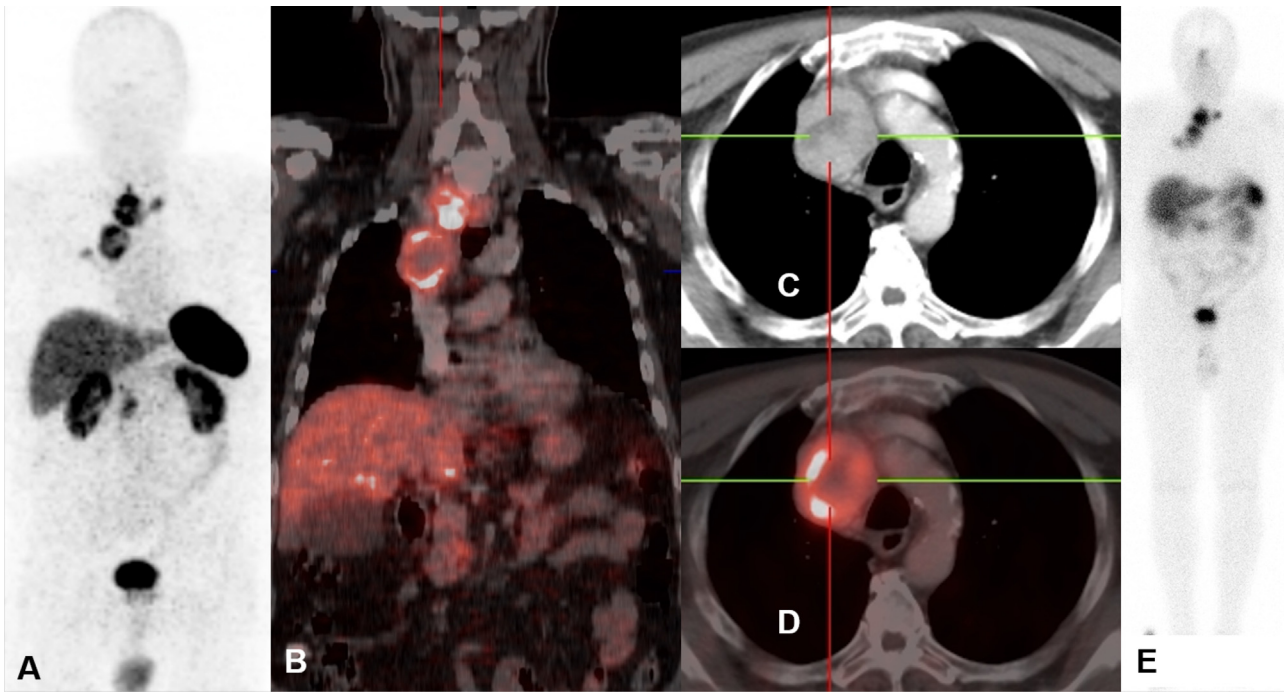

Figure 4 Partial remission of the disease (described in Figure 3) after just one cycle with increasing necrosis, especially in the mediastinal lymph node mass demonstrated by decreasing uptake on follow-up ^{68}Ga-DOTATOC PET/CT (A-D). The patient underwent another cycle of PRRT with ^{177}Lu-DOTATOC, which demonstrated uptake at these sites (E).

especially the high SSTR expression on baseline ^{68}Ga-DOTATOC PET/CT scans and demonstrated the satisfactory therapeutic value of PRRT in SSTR-expressing progressive radioiodine-negative DTC. In addition, they confirmed the diagnostic value ^{68}Ga-labeled somatostatin analogue PET/CT for a personalized treatment approach.[19] The available reports of PRRT in 93 patients with DTC are summarized in Table 2. No definite conclusions can be drawn on the therapeutic efficacy of PRRT in DTC based on available studies, because they applied various exclusion or inclusion and response assessment criteria, different radiopeptides and dissimilar study design.

Nevertheless, it is obvious that PRRT is a safe treatment option for patients with progressing non–iodine avid DTC as only two cases of grade III or IV toxicity have been reported among several hundred PRRT cycles. In addition, its effectiveness is comparable with other therapeutic choices, including biological agents, available for these patients. However, as emphasized by several authors, considering that relatively low fraction of non–iodine avid patients with DTC have high expression of SSTRs on tumoral cells, comprehensive patient selection using ^{68}Ga-DOTA-SSTR PET/CT seems inevitable.[72,73] Furthermore, PET/CT is a reliable tool both for staging and for assessment of therapy response (Figs. 3 and 4).

References

1. American Cancer Society: Cancer Facts & Figures 2015. Atlanta: American Cancer Society; 2015
2. Eustatia-Rutten CF, Corssmit EP, Biermasz NR, et al: Survival and death causes in differentiated thyroid carcinoma. J Clin Endocrinol Metab 2006;91:313-319
3. Sherman SI: Thyroid carcinoma. Lancet 2003;361:501-511
4. Durante C, Haddy N, Baudin E, et al: Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006;91:2892-2899
5. Hundahl SA, Fleming ID, Fremgen AM, et al: A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer 1998;83:2638-2648
6. Antonelli A, Ferri C, Ferrari SM, et al: New targeted molecular therapies for dedifferentiated thyroid cancer. J Oncol 2010;2010. (921682)
7. Ho AL, Grewal RK, Leboeuf R, et al: Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med 2013;368:623-632
8. Thomas L, Lai SY, Dong W, et al: Sorafenib in metastatic thyroid cancer: A systematic review. Oncologist 2014;19:251-258
9. Baudin E, Schlumberger M, Lumbroso J, et al: Octreotide scintigraphy in patients with differentiated thyroid carcinoma: Contribution for patients with negative radioiodine scan. J Clin Endocrinol Metab 1996;81:2541-2544
10. Tenenbaum F, Lumbroso J, Schlumberger M, et al: Radiolabeled somatostatin analog scintigraphy in differentiated thyroid carcinoma. J Nucl Med 1995;36:807-810
11. Christian JA, Cook GJ, Harmer C: Indium-111-labelled octreotide scintigraphy in the diagnosis and management of non-iodine avid metastatic carcinoma of the thyroid. Br J Cancer 2003;89:258-261
12. Haslinghuis LM, Krenning EP, De Herder WW, et al: Somatostatin receptor scintigraphy in the follow-up of patients with differentiated thyroid cancer. J Endocrinol Invest 2001;24:415-422
13. Budiawan H, Salavati A, Kulkarni HR, et al: Peptide receptor radionuclide therapy of treatment-refractory metastatic thyroid cancer using (90) Yttrium and (177)Lutetium labeled somatostatin analogs: Toxicity, response and survival analysis. Am J Nucl Med Mol Imaging 2013;4:39-52
14. Teunissen JJ, Kwekkeboom DJ, Krenning EP: Staging and treatment of differentiated thyroid carcinoma with radiolabeled somatostatin analogs. Trends Endocrinol Metab 2006;17:19-25
15. Iten F, Muller B, Schindler C, et al: Response to [90Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: A phase II clinical trial. Clin Cancer Res 2007;13:6696-6702
16. Gorges R, Kahaly G, Muller-Brand J, et al: Radionuclide-labeled somatostatin analogues for diagnostic and therapeutic purposes in nonmedullary thyroid cancer. Thyroid 2001;11:647-659
17. Czepczynski R, Matysiak-Grzes M, Gryczynska M, et al: Peptide receptor radionuclide therapy of differentiated thyroid cancer: Efficacy and toxicity. Arch Immunol Ther Exp (Warsz) 2015;63:147-154
18. Bodei L, Handkiewicz-Junak D, Grana C, et al: Receptor radionuclide therapy with 90Y-DOTATOC in patients with medullary thyroid carcinomas. Cancer Biother Radiopharm 2004;19:65-71
19. Baum RP, Kulkarni HR: THERANOSTICS: From molecular imaging using Ga-68 labeled tracers and PET/CT to personalized radionuclide therapy—The Bad Berka experience. Theranostics 2012;2:437-447
20. Baum RP, Kulkarni HR, Carreras C: Peptides and receptors in image-guided therapy: Theranostics for neuroendocrine neoplasms. Semin Nucl Med 2012;42:190-207
21. Salavati A, Prasad V, Schneider CP, et al: Peptide receptor radionuclide therapy of Merkel cell carcinoma using (177)lutetium-labeled somatostatin analogs in combination with radiosensitizing chemotherapy: A potential novel treatment based on molecular pathology. Ann Nucl Med 2012;26:365-369
22. Gulenchyn KY, Yao X, Asa SL, et al: Radionuclide therapy in neuroendocrine tumours: A systematic review. Clin Oncol (R Coll Radiol) 2012;24:294-308
23. Kim SJ, Pak K, Koo PJ, et al: The efficacy of Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: A meta-analysis. Eur J Nucl Med Mol Imaging 2015;42:1964-1970
24. van Essen M, Sundin A, Krenning EP, et al: Neuroendocrine tumours: The role of imaging for diagnosis and therapy. Nat Rev Endocrinol 2014;10:102-114
25. Kwekkeboom DJ, de Herder WW, Kam BL, et al: Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: Toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124-2130
26. Reubi JC, Horisberger U, Laissue J: High density of somatostatin receptors in veins surrounding human cancer tissue: Role in tumor-host interaction? Int J Cancer 1994;56:681-688
27. Pazaitou-Panayiotou K, Tiensuu Janson E, Koletsa T, et al: Somatostatin receptor expression in non-medullary thyroid carcinomas. Hormones (Athens) 2012;11:290-296
28. Pisarek H, Pawlikowski M, Marchlewska M, et al: An immunohistochemical investigation of the expression of somatostatin receptor subtypes—Should therapeutic trials be performed to determine the efficacy of somatostatin analogs in treating advanced thyroid malignances? Exp Clin Endocrinol Diabetes 2015;123:342-346
29. Papotti M, Kumar U, Volante M, et al: Immunohistochemical detection of somatostatin receptor types 1-5 in medullary carcinoma of the thyroid. Clin Endocrinol 2001;54:641-649
30. Mussig K, Wehrmann T, Dittmann H, et al: Expression of the proliferation marker Ki-67 associates with tumour staging and clinical outcome in differentiated thyroid carcinomas. Clin Endocrinol 2012;77:139-145
31. Sancak S, Hardt A, Singer J, et al: Somatostatin receptor 2 expression determined by immunohistochemistry in cold thyroid nodules exceeds that of hot thyroid nodules, papillary thyroid carcinoma, and Graves' disease. Thyroid 2010;20:505-511
32. Klagge A, Krause K, Schierle K, et al: Somatostatin receptor subtype expression in human thyroid tumours. Horm Metab Res 2010;42:237-240
33. Pisarek H, Stepien T, Kubiak R, et al: Expression of somatostatin receptor subtypes in human thyroid tumors: The immunohistochemical and molecular biology (RT-PCR) investigation. Thyroid Res 2009;2:1
34. Druckenthaner M, Schwarzer C, Ensinger C, et al: Evidence for somatostatin receptor 2 in thyroid tissue. Regul Pept 2007;138:32-39

35. Forssell-Aronsson EB, Nilsson O, Bejegard SA, et al: 111In-DTPA-D-Phe1-octreotide binding and somatostatin receptor subtypes in thyroid tumors. J Nucl Med 2000;41:636-642
36. Ain KB, Taylor KD, Tofiq S, et al: Somatostatin receptor subtype expression in human thyroid and thyroid carcinoma cell lines. J Clin Endocrinol Metab 1997;82:1857-1862
37. Appetecchia M, Baldelli R: Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumours, current aspects and new perspectives. J Exp Clin Cancer Res 2010;29:19
38. Kohlfuerst S, Igerc I, Gallowitsch HJ, et al: Is there a role for sandostatin treatment in patients with progressive thyroid cancer and iodine-negative but somatostatin-receptor-positive metastases? Thyroid 2006;16:1113-1119
39. Zlock DW, Greenspan FS, Clark OH, et al: Octreotide therapy in advanced thyroid cancer. Thyroid 1994;4:427-431
40. Hoelting T, Duh QY, Clark OH, et al: Somatostatin analog octreotide inhibits the growth of differentiated thyroid cancer cells in vitro, but not in vivo. J Clin Endocrinol Metab 1996;81:2638-2641
41. Zatelli MC, degli Uberti EC: Somatostatin receptors: From basic science to clinical approach—Thyroid. Dig Liver Dis 2004;36:S86-92 (suppl 1)
42. Bauer W, Briner U, Doepfner W, et al: SMS 201-995: A very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982;31:1133-1140
43. Valkema R, De Jong M, Bakker WH, et al: Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: The Rotterdam experience. Semin Nucl Med 2002;32:110-122
44. Stokkel MP, Verkooijen RB, Bouwsma H, et al: Six month follow-up after 111In-DTPA-octreotide therapy in patients with progressive radioiodine non-responsive thyroid cancer: A pilot study. Nucl Med Commun 2004;25:683-690
45. van Essen M, Krenning EP, Kam BL, et al: Peptide-receptor radionuclide therapy for endocrine tumors. Nat Rev Endocrinol 2009;5:382-393
46. Wild D, Schmitt JS, Ginj M, et al: DOTANOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. Eur J Nucl Med Mol Imaging 2003;30:1338-1347
47. Wehrmann C, Senftleben S, Zachert C, et al: Results of individual patient dosimetry in peptide receptor radionuclide therapy with 177Lu DOTA-TATE and 177Lu DOTANOC. Cancer Biother Radiopharm 2007;22:406-416
48. Prasad V, Fetscher S, Baum RP: Changing role of somatostatin receptor targeted drugs in NET: Nuclear medicine's view. J Pharm Pharm Sci 2007;10:321s-337s
49. Schuchardt C, Kulkarni HR, Prasad V, et al: The Bad Berka dose protocol: Comparative results of dosimetry in peptide receptor radionuclide therapy using (177)Lu-DOTATATE, (177)Lu-DOTANOC, and (177)Lu-DOTA-TOC. Recent Results Cancer Res 2013;194:519-536
50. Wild D, Fani M, Fischer R, et al: Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: A pilot study. J Nucl Med 2014;55:1248-1252
51. Wild D, Fani M, Behe M, et al: First clinical evidence that imaging with somatostatin receptor antagonists is feasible. J Nucl Med 2011;52:1412-1417
52. Ginj M, Zhang H, Waser B, et al: Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors. Proc Natl Acad Sci U S A 2006;103:16436-16441
53. Dalm SU, Nonnekens J, Doeswijk GN, et al: Comparison of the therapeutic response to treatment with a 177-lutetium labeled somatostatin receptor agonist and antagonist in preclinical models. J Nucl Med 2015 (Epub ahead of print)
54. Chatalic KL, Kwekkeboom DJ, de Jong M: Radiolabeled peptides for imaging and therapy: A radiant future. J Nucl Med 2015;56:1809-1812
55. Modigliani E, Cohen R, Campos JM, et al: Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: Results in 899 patients. The GETC Study Group. Groupe d'etude des tumeurs a calcitonine. Clin Endocrinol 1998;48:265-273
56. Laure Giraudet A, Al Ghulzan A, Auperin A, et al: Progression of medullary thyroid carcinoma: Assessment with calcitonin and carcinoembryonic antigen doubling times. Eur J Endocrinol 2008;158:239-246
57. Giraudet AL, Vanel D, Leboulleux S, et al: Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J Clin Oncol 2007;92:4185-4190
58. Martins RG, Rajendran JG, Capell P, et al: Medullary thyroid cancer: Options for systemic therapy of metastatic disease? J Clin Oncol 2006;24:1653-1655
59. Wells SA Jr, Robinson BG, Gagel RF, et al: Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial. J Clin Oncol 2012;30:134-141
60. Mato E, Matias-Guiu X, Chico A, et al: Somatostatin and somatostatin receptor subtype gene expression in medullary thyroid carcinoma. J Clin Endocrinol Metab 1998;83:2417-2420
61. Hofland LJ, Lamberts SW: Somatostatin receptors and disease: Role of receptor subtypes. Baillieres Clin Endocrinol Metab 1996;10:163-176
62. Kwekkeboom DJ, Reubi JC, Lamberts SW, et al: In vivo somatostatin receptor imaging in medullary thyroid carcinoma. J Clin Endocrinol Metab 1993;76:1413-1417
63. Berna L, Chico A, Matias-Guiu X, et al: Use of somatostatin analogue scintigraphy in the localization of recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging 1998;25:1482-1488
64. Frank-Raue K, Ziegler R, Raue F: The use of octreotide in the treatment of medullary thyroid carcinoma. Horm Metab Res Suppl 1993;27:44-47
65. Lupoli G, Cascone E, Arlotta F, et al: Treatment of advanced medullary thyroid carcinoma with a combination of recombinant interferon alpha-2b and octreotide. Cancer 1996;78:1114-1118
66. Vitale G, Tagliaferri P, Caraglia M, et al: Slow release lanreotide in combination with interferon-alpha2b in the treatment of symptomatic advanced medullary thyroid carcinoma. J Clin Endocrinol Metab 2000;85:983-988
67. Waldherr C, Schumacher T, Pless M, et al: Radiopeptide transmitted internal irradiation of non-iodophil thyroid cancer and conventionally untreatable medullary thyroid cancer using. Nucl Med Commun 2001;22:673-678
68. Vaisman F, de Castro PH, Lopes FP, et al: Is there a role for peptide receptor radionuclide therapy in medullary thyroid cancer? Clin Nucl Med 2015;40:123-127
69. Makis W, McCann K, McEwan AJ: Medullary thyroid carcinoma (MTC) treated with 177Lu-DOTATATE PRRT: A report of two cases. Clin Nucl Med 2015;40:408-412
70. Young H, Baum R, Cremerius U, et al: Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: Review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 1999;35:1773-1782
71. Kulkarni HR, Baum RP: Theranostics with Ga-68 somatostatin receptor PET/CT: Monitoring response to peptide receptor radionuclide therapy. PET Clin 2014;9:91-97
72. Versari A, Sollini M, Frasoldati A, et al: Differentiated thyroid cancer: A new perspective with radiolabeled somatostatin analogues for imaging and treatment of patients. Thyroid 2014;24:715-726
73. Jois B, Asopa R, Basu S: Somatostatin receptor imaging in non-(131)I-avid metastatic differentiated thyroid carcinoma for determining the feasibility of peptide receptor radionuclide therapy with (177)Lu-DOTATATE: Low fraction of patients suitable for peptide receptor radionuclide therapy and evidence of chromogranin A level-positive neuroendocrine differentiation. Clin Nucl Med 2014;39:505-510
74. Chinol M, Bodei L, Cremonesi M, et al: Receptor-mediated radiotherapy with Y-DOTA-DPhe-Tyr-octreotide: The experience of the European Institute of Oncology Group. Semin Nucl Med 2002;32:141-147
75. Virgolini I, Britton K, Buscombe J, et al: In- and Y-DOTA-lanreotide: Results and implications of the MAURITIUS trial. Semin Nucl Med 2002;32:148-155
76. Gabriel M, Froehlich F, Decristoforo C, et al: 99mTc-EDDA/HYNIC-TOC and (18)F-FDG in thyroid cancer patients with negative (131)I whole-body scans. Eur J Nucl Med Mol Imaging 2004;31:330-341
77. Teunissen JJ, Kwekkeboom DJ, Kooij PP, et al: Peptide receptor radionuclide therapy for non-radioiodine-avid differentiated thyroid carcinoma. J Nucl Med 2005;46:107S-114S (suppl 1)
78. Campenni A, Pignata SA, Baldari S: Can peptide receptor radionuclide therapy (PRRT) be useful in radioiodine-refractory differentiated thyroid cancer? Endocrine 2015;50:516-518