İSTANBUL ÜNİVERSİTESİ YAYINEVİ

RESEARCH / ARAŞTIRMA
DOI: 10.26650/IUITFD.2019.0097
İst Tıp Fak Derg 2020 / J Ist Faculty Med 2020

AN ALTERNATIVE THERAPY OPTION IN METASTATIC THYROID CANCER: PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

METASTATİK TİROİD KANSERİNDE ALTERNATİF TEDAVİ SEÇENEĞİ: PEPTİD RESEPTÖR RADYONÜKLİD TEDAVİ

Havva YEŞİL ÇINKIR[1], Umut ELBOĞA[2]

Gaziantep University, Faculty of Medicine, [1]Department of Medical Oncology, [2]Department of Nuclear Medicine, Gaziantep, Turkey

ORCID IDs of the authors: H.Y.Ç. 0000-0002-7870-8741; U.E. 0000-0002-3650-8258

Cite this article as: Yesil Cinkir, H, Elboga U. An alternative therapy option in metastatic thyroid cancer: peptide receptor radionuclide therapy. J Ist Faculty Med 2020;83(4):339-44. doi: 10.26650/IUITFD.2019.0097

ABSTRACT

Objective: In this study, we aimed to evaluate the results of peptide receptor radionuclide therapy (PRRT) in the treatment of metastatic thyroid cancer patients.

Material and Method: In total, 10 patients with metastatic thyroid cancer treated with PRRT were evaluated. There were 5 medullary thyroid cancer (MTC) patients and 5 patients had differentiated thyroid cancer (DTC).

Results: Median age at first PRRT was 61.5 (38-79) years and 5/10 (50%) were female. The mean overall survival (OS) was 19.2 months (95% CI; 4.1-34.3) after the first PRRT. The mean progression-free survival (PFS) was 4.5 months (95% CI; 2.8-6.3). According to pathologic subgroup analysis, the mean OS were 13.8 months (95% CI; 4.0-23.7) in DTC and 24.2 (95% CI; 0-48.8) in MTC after first PRRT (p:0.555). Five patients had stable disease and one patient had partial response. Minor hematological toxicity was observed in 4 patients.

Conclusion: PRRT appears to be an alternative treatment option for thyroid cancer. It is thought that the results will be more desirable as the patients take the treatment in the earlier stages.

Keywords: Radionuclide therapy, survival, thyroid cancer

ÖZET

Amaç: Bu çalışmada, metastatik tiroid kanserli hastaların tedavisinde peptid reseptörü radyonüklid tedavisinin (PRRT) sonuçlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: PRRT ile tedavi edilen metastatik tiroid kanseri olan 10 hasta değerlendirildi. Beş medüller tiroid karsinomu (MTC) ve 5 differansiye tiroid karsinomu (DTC) mevcuttu.

Bulgular: İlk PRRT uygulamasında ortalama yaş 61,5 (38-79) yıl ve hastaların 5/10 (%50)'u kadındı. Ortalama genel sağkalım (GSK), ilk PRRT' den sonra 19,2 ay (%95 CI; 4,1-34,3) idi. Ortalama progresyonsuz sağkalım 4,5 aydı (%95 CI; 2,8-6,3). Patolojik alt grup analizine göre ilk PRRT sonrası ortalama GSK; DTC'de 13,8 ay (%95 CI; 4,0-23,7) ve MTC'de 24,2 (%95 CI; 0-48,8) idi (p:0.555). Beş hastada stabil hastalık, bir hastada kısmi yanıt saptandı. Dört hastada minör hematolojik toksisite gözlendi.

Sonuç: PRRT tiroid kanseri için alternatif bir tedavi seçeneği olarak görünmektedir. Hastaların tedaviyi erken evrelerde almasıyla sonuçların daha iyi olacağı düşünülmektedir.

Anahtar Kelimeler: Radyonüklid tedavi, sağkalım, tiroid kanseri

INTRODUCTION

Thyroid cancer is a common malignancy of the head and neck region, whose incidence rate has been increasing in recent years (1). Differentiated type of thyroid cancer (DTC) (follicular and papillary) has an excellent 10-year survival rate of 85-99% and the postoperative recurrence rate of 23-30% (2, 3). Medullary thyroid cancer (MTC) is often associated with multiple endocrine neoplasia and represents approximately 3% of thyroid cancers (4). The 5-year relative survival of MTC is 93% for stage I to III, and 28% for stage IV (5). The conventional treatment options alter depending on the subtype and stage of the cancer. These options for thyroid cancer include surgery, radioactive iodine (^{131}I)

Corresponding author/İletişim kurulacak yazar: drhavva1982@gmail.com

Submitted/Başvuru: 02.12.2019 • **Revision Requested/Revizyon Talebi:** 30.01.2020 •
Last Revision Received/Son Revizyon: 30.03.2020 • **Accepted/Kabul:** 01.05.2020 • **Published Online/Online Yayın:** 22.09.2020

©Telif Hakkı 2020 J Ist Faculty Med - Makale metnine jmed.istanbul.edu.tr web sayfasından ulaşılabilir.
©Copyright 2020 by J Ist Faculty Med - Available online at jmed.istanbul.edu.tr

(RAI) therapy, radiotherapy (RT), and targeted therapy with several tyrosine kinase inhibitors (TKIs). The presence of somatostatin receptors in endocrin tumors has been demonstrated in DTC and MTC (6, 7). Therefore, the use of somatostatin analogs as ligands and targeting of the tumor with a radionuclide appears to be an attractive option. In this study, we aimed to analyse the results of peptide receptor radionuclide therapy (PRRT) in the treatment of patients with metastatic thyroid cancer.

MATERIAL AND METHOD

Study design and patients

In total, 10 patients (MTC: 5, papillary thyroid cancer (PTC): 4, follicular thyroid cancer (FTC): 1) treated with PRRT were evaluated at the Gaziantep University Faculty of Medicine between 2015-2019, retrospectively. The inclusion criteria for the study were; diagnosis of a histopathologically confirmed DTC or MTC, age ≥18 years, an available clinicopathological and follow-up data, occurrence of non-regional lymh nodes or distant metastases, non-RAI-avid or RAI refractory DTC, progression on previous treatments (chemotherapy, radiotherapy or TKIs), presence of visible somatostatin receptor expression at the ^{68}Ga labelled DOTATATE (synthetic somatostatin analogue peptide) positron emission tomography (PET). The exclusion criteria were; presence of cardiac, hepatic, hematological and renal dysfunctions, occurence of other malignant tumors.

The study was approved by the ethics committee of the Gaziantep University (Decision no: 2019/316, date: 28.08.2019). From all patients, written informed consent was obtained before the administration of radiolabeled substances.

Peptide receptor radionuclide therapy

Firstly, ^{68}Ga labelled DOTATATE (synthetic somatostatin analogue peptide) PET was performed and SSTR expression was detected. The existence of an SSTR led us to consider that ^{177}Lutetium (^{177}Lu) labelled DOTATATE could be used as an alternative treatment. The infused dose of ^{177}Lu labelled DOTATATE was 200 mCi. The treatment was applied at 6-10 weeks intervals.

Before initiating the ^{177}Lu labelled DOTATATE treatment, hematological and renal function tests were analyzed. The inclusion criteria for performing PRRT were hemoglobin ≥10 g/dL, white blood cell (leukocyte) count ≥4x10^3/μL, platelet count ≥100x10^3/μL, serum creatinine ≤1.2 mg/dL or creatinine clearance ≥60 mL/min, and Eastern Cooperative Oncology Group (ECOG) performans status (PS) ≤2.

For protecting renal function, the fluid protocol performed before and after ^{177}Lu labelled DOTATATE treatment was as follows: 750 miligram magnesium sulfate and 10 mg metoclopramide were injected into a 1000 cc ringer lactate solution, and applied over 60-75 minutes.

Response assesment was performed after treatment of ≥2 cycles based on standardized uptake value (SUV) max (8). The responses were: complete metabolic response, partial metabolic response (PR) (decrease with 15-25%), stable disease (SD) (no change or decrease with 15%) and progressive metabolic disease (P) (new lesions or increase of >25%).

Common Terminology Criteria for Adverse Events (CTCAE) was used for adverse events scoring.

Statistical analysis

The outcomes of treatment were progression-free survival (PFS), overall survival (OS), response rates and toxicities. PFS was described as the interval from treatment initiation to progression, last documented patient visit or death. OS was defined as the time between treatment initiation and death or until the last documented patient visit. The Kaplan-Meier method and Log-rank statistics were used for survival analysis. $P<0.05$ was defined as statistically significant. The Statistical Package for Social Sciences version 22.0 for Windows (SPSS, Inc. Chicago, IL, USA) was performed for all statistical analyzes.

RESULTS

Ten patients were treated with ^{177}Lu labelled DOTATATE. The clinical characteristics of patients are summarized in Table 1. The median age was 61.5 (38-79) years at first PRRT, and 5/10 (50%) were females. Nine out of the 10 (90%) patients had a baseline ECOG PS of 0-1. None of the patients had an endocrine paraneoplastic syndrome. A total thyroidectomy was performed in all patients. All the patients had metastasis to the lymph nodes, 8 patients had bone and 6 patients had lung metastases.

Of the 10 patients, 5 have (3 of PTC, 2 of MTC) died. Response assessment was performed in 7 patients who were treated with >2 cycles. The remaining 3 patients were excluded. Two patients died after first and second therapy, one patient was lost to follow up. 5 patients had SD and one patient had PR. Progression was observed in one patient.

The mean and the median OS were 19.2 months (95% CI; 4.1-34.3) and 9.1 months (95% CI; 0-25.2) after the first PRRT (Figure 1). The mean and the median OS were 90.5 months (95% CI; 67.1-113.8) and 94.7 months (95% CI; 56.7-132.6) after the diagnosis. The mean and the median PFS were 4.5 months (95% CI; 2.8-6.3) and 2.9 months (95% CI; 0.9-5.0) (Figure 2).

In total, ten patients received 31 PRRT courses. Minor hematological toxicity was detected in 4 patients. Leukopenia (CTCAE grade I) was observed in 3 patients. Anemia (CTCAE grade 2) was observed in one patient and grade

Table 1: Patient's characteristics, baseline data, and status after the last PRRT

	1	2	3	4	5	6	7	8	9	10
Gender	**M**	**F**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Tumor type	MTC	MTC	MTC	MTC	MTC	PTC	PTC	PTC	FTC	PTC
Previous treatments	T, ND, CT, RT, TKIs	T, ND	T, ND, CT, RT, TKIs	T, ND, CT, TKIs	T, ND, CT, TKIs	T, ND, RAI, TKIs	T, ND, RAI, TKIs	T, ND, RAI, TKIs	T, ND, RAI, TKIs	T, ND, RAI, TKIs
Stage	IV_C	IV_C	IV_C	IV_C	IV_C	IV_B	IV_B	IV_B	IV_B	II
Age at 1st PRRT	59	79	53	59	38	64	77	64	67	49
PRRT line	6	1	6	5	3	3	3	4	3	5
PRRT course	2	4	6	4	2	3	1	4	3	2
Metastases before PRRT	Lo, L, B, LAP	Lo, LAP	L, B, LAP	LAP	B, LAP	L, B, LAP	L, B, LAP	L, B, LAP	L, B, LAP	Lo, B, LAP
PRRT response	Unkn	Unkn	S	S	S	PR	Unkn	P	S	S
Status after last PRRT	E	A	E	A	A	E	E	A	A	E

A: Alive, B: Bone, CT: Chemotherapy, E: Exitus, F: Female, FTC: Follicular thyroid cancer, L: Lung, LAP: Lymph node involvement, Lo: Local, M: Male, MTC: Medullary thyroid cancer, ND: Neck dissection, P: Progression, PR: Partial response, PRRT: Peptide receptor radionuclide therapy, PTC: Papillary thyroid cancer, RAI: Radioactive iodine, RT: Radiotherapy, S: Stable, Unkn: Unknown, T: Thyroidectomy, TKIs: Tyrosine kinase inhibitors

I was in one patient. None of the patients experienced thrombocytopenia. None of the patients experienced hepatotoxicity or nephrotoxicity.

According to pathologic subgroup analysis;

DTC: The median age was 64 (49-77) years at first PRRT. They recevied radioiodine therapies and TKIs before

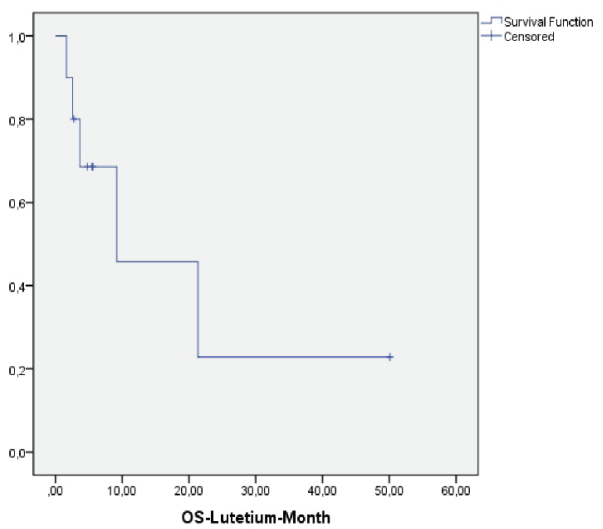

Figure 1: Kaplan-Meier analysis: mean overall survival after the first PRRT cycle was 19.2 months (95% CI; 4.1-34.3).

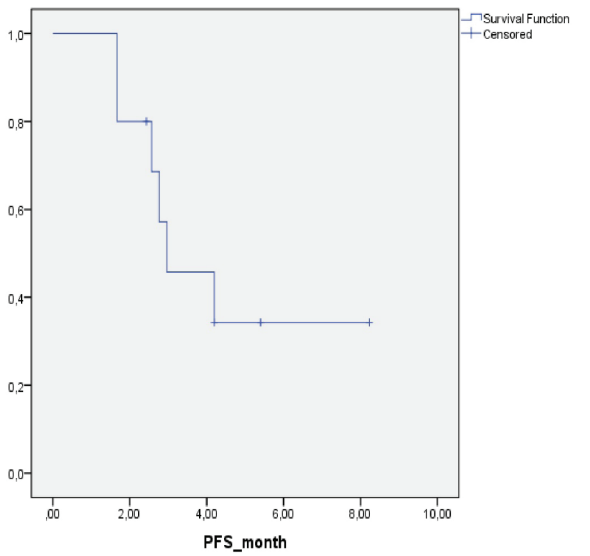

Figure 2: Kaplan-Meier analysis: mean progression free survival 4.5 months (95% CI; 2.8-6.3).

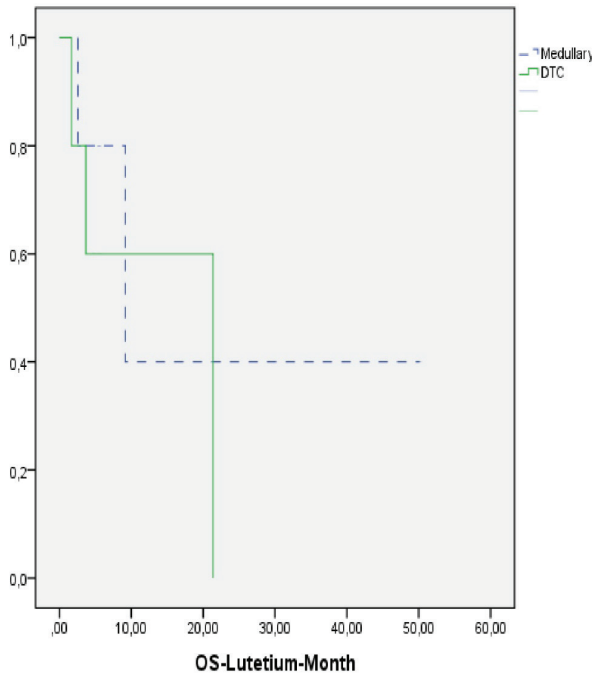

Figure 3: Mean overall survival (OS) were 13.8 months (95% CI; 4.0-23.7) in DTC and 24.2 (95% CI; 0-48.8) in MTC after first PRRT (p=0.555).

PPRT: The mean OS was 13.8 months (95% CI; 4.0-23.7) after first PRRT (Figure 3, p=0.555). The mean PFS was 5.5 months (95% CI; 1.7-9.4).
MTC: At first PRRT, the median age was 59 (38-79) years. The germline mutation of RET proto-oncogene was not determined. They recevied chemotherapy, radiotherapy (RT) and TKIs before PRRT. The mean OS was 24.2 (95% CI; 0-48.8) after first PRRT (Figure 3, p=0.555). The mean PFS was 37.3 months (95% CI; 17.6-56.9).

DISCUSSION

Thyroid cancers' prognosis and treatment depend on the type and stage of the tumor at diagnosis. Since thyroid cells have been shown to express SSTR, radionuclide applications have been the treatment of choice (6, 9). In the light of this information, we aimed to present the interim results of patients with thyroid cancer who underwent radionuclide therapy in our center.

An absence of SSTR2a expression in the tissue biopsy might be a poor prognostic sign in MTC (9). A low level of SSTR2a expression was associated with poor outcome and more aggressive grades of tumor in gastroenteropancreatic neuroendocrine tumors (10). The 10-year survival rates in stage IV MTC patients were 96% in SSTR2a positive patients and 43% in SSTR2a negative patients (11). ^{111}In-DTPA-octreotide scans were used to analyse SSTR2a uptake in 35 non-treated patients (10). Nowadays, ^{68}Ga-DOTATATE PET scan has been utilized more frequently. It has imaging advantages. These are excate staging of the patient, and presences of pharmacological (higher affinity to SSTR2a), physical (higher gamma energies) and technical (e.g. positron imaging, attenuation correction) differences (12). In our hospital, we used ^{68}Ga-DOTATATE PET for demonstrating the SSTR expression. After this procedure, patients with positive involvement were treated.

Survival is increased and recurrence rates are decreased with total thyroidectomy. Treatment with radioactive iodine (RAI) has been an integral adjuvant role in the DTC. The risk of recurrence in DTC is 30%, and 66% of these relapses are in the first decade after initial treatment (8). Also, RAI therapy is the backbone of treatment in recurrence. Iodine-avidity of metastases is a very significant prognostic factor in DTC. The OS rate of patients with non-RAI-avid is notably lower than that of patients with iodine-avid lesions (13-15). Unfortunately, treatment options are limited in patients non-RAI-avid or resistant to this treatment. Systemic treatment such as with TKIs is another alternative. However, TKIs cause severe side-effects, and these drugs can decrease quality of life and beginning with this as a treatment option should be carefully considered (16). Therefore, there is a demand for new treatment modalities for this group of patients. The fact that SSTR expression is defined in DTC has been an alternative treatment option in these patients (17-19). Our patients had received other standard treatments and PRRT was applied upon progression observation. The response rates reported in the literature were 30-80% in patients with DTC (17, 20). In our study, the rate of disease control was 75% (2=stable response, 1=partial response), which was similar to previous studies.

Like DTC, locally advanced tumor or distant metastases have limited systemic treatment options in MTC. Conventional chemotherapy has an inadequate efficacy and treatment-related toxicity rates are high (21). With advances in tumor biology, treatments such as vandetanib and cabozantinib, and a tyrosine kinase inhibitor that targets the RET proto-oncogene, have been used in clinical practice (22, 23). An increase in survival was reported with these treatments, but grade 3-4 side effects were observed in most patients (vandetanib=44%, cabozantinib=69%). Therefore, alternative treatment options with fewer side effects were needed. With the detection of SSTR expression in MTC, PPRT has become the new treatment option (9). According to previous studies, the response rates were 29-80%, in our study we found stable disease response in all 3 patients who underwent treatment response evaluation (18, 24).

In our study, the mean PFS and OS were in favor of MTC. According to the literature, the survival rate for MTC is not as good as for differentiated thyroid cancer (25). However, our results were the exact opposite of the literature. This demonstrates that our patient's population had more aggressive characteristics.

The median treatment line was 3.5 (range, 1-6) for all patients (DTC=3, range, 3-5; MTC=5, range, 1-6). Survival data were poor due to the fact that PRRT was applied in advanced stages for both DTC and MTC patients. Previous studies have suggested that PRRT should be used in the early stages (26, 27). It has been advocated that success rates may increase with the combined use of chemotherapy agents that increase radiation sensitivity. In our study, all patients were unresponsive to other treatments and PRRT was the last treatment option. Exceptionally, PRRT was administered as an initial treatment in an elderly patient (age, 79 years). PRRT, which is considered to be less toxic, was applied because the patient was of advanced age and did not accept other conventional treatments.

Treatment-induced toxicity both reduces treatment success and creates incompatibility. Radiolabelled somatostatin analogues are an important risk for nephrotoxicity. In previous studies, renal protection could be achieved by infusion of amino acid solutions and by monitoring the radiation dose to the kidney to a maximum of 23-27 Gy (28, 29). We also applied a protocol including fluid replacement and anti-emetic treatment to our patients for renal protection. Hematological toxicity is another important side effect. In our results, the patients tolerated the treatment well and we did not observe CTCAE grade >2 toxicity.

There were restrictive aspects of our study. The first factor was the small sample size of patients. Secondly, the patient group was heterogeneous. Thirdly, the follow-up time was quite short. The number of patients who started treatment has increased in the last 2 years. Therefore, the results of the patients were more negative than previous reports.

CONCLUSION

PRRT appears to be an alternative treatment option for thyroid cancer. It is thought that the results will be more desirable as the patients take the treatment in the earlier stages.

Ethics Committee Approval: This study was approved by the Ethical Committee of the Gaziantep University (Decision no: 2019/316).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- H.Y.Ç., U.E.; Data Acquisition- H.Y.Ç., U.E.; Data Analysis/Interpretation- H.Y.Ç., U.E.; Drafting Manuscript- H.Y.Ç.; Critical Revision of Manuscript- H.Y.Ç., U.E.; Final Approval and Accountability- H.Y.Ç., U.E.; Supervision- H.Y.Ç., U.E.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Gaziantep Üniversitesi Etik Kurulu'ndan alınmıştır (Karar no: 2019/316).

Bilgilendirilmiş Onam: Katılımcılardan bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- H.Y.Ç., U.E.; Veri Toplama- H.Y.Ç., U.E.; Veri Analizi/Yorumlama- H.Y.Ç., U.E; Yazı Taslağı- H.Y.Ç.; İçeriğin Eleştirel İncelemesi- H.Y.Ç., U.E.; Son Onay ve Sorumluluk- H.Y.Ç., U.E.; Süpervizyon- H.Y.Ç., U.E.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

REFERENCES

1. Mao Y, Xing M. Recent incidences and differential trends of thyroid cancer in the USA. Endocr Relat Cancer 2016;23:313-22. [CrossRef]
2. Eustatia-Rutten CF, Corssmit EP, Biermasz NR, Pereira AM, Romijn JA, Smit JW. Survival and death causes in differentiated thyroid carcinoma. J Clin Endocrinol Metab 2006;91(1):313-9. [CrossRef]
3. Yang X, Liang J, Li TJ, Yang K, Liang DQ, Yu Z, et al. Postoperative stimulated thyroglobulin level and recurrence risk stratification in differentiated thyroid cancer. Chin Med J 2015;128(8):1058-64. [CrossRef]
4. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer: the American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2009;19(11):1167-214. [CrossRef]
5. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer 1998;83(12):2638-48. [CrossRef]
6. Klagge A, Krause K, Schierle K, Steinert F, Dralle H, Fuhrer D. Somatostatin receptor subtype expression in human thyroid tumours. Horm Metab Res 2010;42(4):237-40. [CrossRef]
7. Papotti M, Croce S, Bello M, Bongiovanni M, Allia E, Schindler M, et al. Expression of somatostatin receptor types 2, 3 and 5 in biopsies and surgical specimens of human lung tumours. Correlation with preoperative octreotide scintigraphy. Virchows Arch 2001;439(6):787-97. [CrossRef]

8. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97(5):418-28. [CrossRef]
9. Beukhof CM, Brabander T, Nederveen FH, Velthuysen ML, de Rijke YB, Hofland LJ, et al. Peptide receptor radionuclide therapy in patients with medullary thyroid carcinoma: predictors and pitfalls. BMC Cancer 2019;19(1):325. [CrossRef]
10. Wang Y, Wang W, Jin K, Fang C, Lin Y, Xue L, et al. Somatostatin receptor expression indicates improved prognosis in gastroenteropancreatic neuroendocrine neoplasm, and octreotide longacting release is effective and safe in Chinese patients with advanced gastroenteropancreatic neuroendocrine tumors. Oncol Lett 2017;13(3):1165-74. [CrossRef]
11. de Vries LH, Lodewijk L, Willems SM, Dreijerink KMA, de Keizer B, van Diest PJ, et al. SSTR2A expression in medullary thyroid carcinoma is correlated with longer survival. Endocrine 2018;62(3):639-47. [CrossRef]
12. Ruf J, Heuck F, Schiefer J, Denecke T, Elgeti F, Pascher A, et al. Impact of multiphase 68Ga-DOTATOC-PET/CT on therapy management in patients with neuroendocrine tumors. Neuroendocrinology 2010;91(1):101-9. [CrossRef]
13. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, 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(8):2892-99. [CrossRef]
14. Baudin E and Schlumberger M. New therapeutic approaches for metastatic thyroid carcinoma. Lancet Oncol 2007;8(2):148-56. [CrossRef]
15. Biermann K, Biersack HJ, Sabet A, Janzen V. Alternative therapeutic approaches in the treatment of primary and secondary dedifferentiated and medullary thyroid carcinoma. Semin Nucl Med 2011;41(2):139-48. [CrossRef]
16. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26(1):1-133. [CrossRef]
17. Budiawan H, Salavati A, Kulkarni HR, Baum RP. 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(1):39-52.
18. Salavati A, Puranik A, Kulkarni HR, Budiawan H, Baum RP. Peptide receptor radionuclide therapy (PRRT) of medullary and nonmedullary thyroid cancer using radiolabeled somatostatin analogues. Semin Nucl Med 2016;46(3):215-24. [CrossRef]
19. Ain KB, Taylor KD, Tofiq S, Venkataraman G. Somatostatin receptor subtype expression in human thyroid and thyroid carcinoma cell lines. J Clin Endocrinol Metab 1997;82(6):1857-62. [CrossRef]
20. Versari A, Sollini M, Frasoldati A, Fraternali A, Filice A, Froio A, et al.Differentiated thyroid cancer:a new perspective with radiolabeled somatostatin analogues for imaging and treatment of patients. Thyroid 2014;24(4):715-26. [CrossRef]
21. Martins RG, Rajendran JG, Capell P, Byrd DR, Mankoff DA. Medullary thyroid cancer: options for systemic therapy of metastatic disease? J Clin Oncol 2006;24(11):1653-5. [CrossRef]
22. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, et al. Activity of XL184 (Cabozantinib), an Oral Tyrosine Kinase Inhibitor, in Patients With Medullary Thyroid Cancer. J Clin Oncol 2011;29(19):2660-6. [CrossRef]
23. Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al.Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, doubleblind phase III trial. J Clin Oncol 2012;30(2):134-41. [CrossRef]
24. Iten F, Müller B, Schindler C, Rochlitz C, Oertli D, Mäcke HR, 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(22 pt 1):6696-702. [CrossRef]
25. Sippel RS, Kunnimalaiyaan M, Chen H. Current management of medullary thyroid cancer. Oncologist 2008;13(5):539-47. [CrossRef]
26. Salavati A, Prasad V, Schneider CP, Herbst R, Baum RP. 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(4):365-9. [CrossRef]
27. Schmidt MC, Uhrhan K, Markiefka B, Hasselbring L, Schlaak M, Cremer B, et al. (68)Ga-DotaTATE PET-CT followed by Peptide Receptor Radiotherapy in combination with capecitabine in two patients with Merkel Cell Carcinoma. Int J Clin Exp Med 2012;5(4):363-6.
28. Rolleman EJ, Valkema R, de Jong M, Kooij PP, Krenning EP. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging 2003;30(1):9-15. [CrossRef]
29. Krenning EP, Kwekkeboom DJ, Valkema R, Pauwels S, Kvols LK, Jong M. Peptide Receptor Radionuclide Therapy. Ann. N.Y. Acad. Sci. 2004;1014:234-45. [CrossRef]