Efficacy and safety of peptide receptor radionuclide therapy in advanced radioiodine-refractory differentiated thyroid cancer and metastatic medullary thyroid cancer: a systematic review

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Abstract

Background: It has been shown that a subgroup of patients with differentiated thyroid cancer (DTC) and medullary thyroid carcinoma (MTC) would progress to advanced stages of thyroid cancer. Therefore, the present study was done to systematically review available evidence in order to investigate efficacy and safety of peptide receptor radionuclide therapy (PRRT) in the patients with advanced radioiodine refractory differentiated thyroid cancer (RR-DTC) and metastatic MTC.

Methods: For this purpose, relevant studies investigated safety and efficacy of PRRT in the patients with advanced RR-DTC and metastatic MTC were identified by searching Medline (Pubmed, Ovid, and Ebsco), Scopus, Embase, Web of Science, and Cochrane Library databases (from database inception to March 24, 2021). The review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Searching was done independently by two investigators. Two researchers independently extracted the data and any disagreement was adjudicated by consensus. Quality of the studies was assessed using the tool of case reports/series in systematic reviews.

Results: Among 2284 related papers, 41 papers met the inclusion criteria. A total of 157 patients with RR-DTC were treated with PPRT. Biochemical and objective responses (partial and complete) were observed in 25.3 and 10.5% of patients, respectively. Among 220 patients with metastatic MTC, biochemical and objective responses were observed in 37.2 and 10.6% of the patients, respectively. Forty-six deaths were reported in 95 patients with advanced RR-DTC. In addition, 63 deaths were observed in 144 patients with metastatic MTC. Major side effects were reported in 124 patients treated with 90Y -based agent. In the patients treated with 177Lu-DOTA-TATE and 111In-Octreotide, mild and transient hematologic or renal complications were reported.

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Background
Thyroid cancer is the most common endocrine malignancy and its incidence has increased by 4.4% per year during 2007–2011 [1, 2]. Differentiated thyroid cancer (DTC), is the most frequent subtype of thyroid cancer accounting for 85–95% of the cases [3, 4]. Medullary thyroid cancer (MTC) originating from parafollicular or C cells of the thyroid gland accounts for approximately 5% of all thyroid cancer cases [5].

The standard of treatment for most patients with DTC includes thyroidectomy followed by radioiodine treatment. A 10-year overall survival rate of 80–99% has been reported among these patients [6]. However, in spite of highly effective treatment strategies, there is a chance of recurrence in 20% of the subjects. Radioactive iodine plays a major role in diagnosis and treatment of recurrent disease [7]. However, some thyroid cancers are resistant to radioiodine despite the elevated level of thyroglobulin [8]. Radioiodine refractory-DTC (RR-DTC) has shown aggressive clinical behavior and a 10-year survival rate of 10% [9, 10]. Surgery and external beam radiation therapy can be used to manage local disease but not in case of widespread metastases. Moreover, chemotherapeutic agents have shown limited efficacy with considerable side effects [11, 12].

MTC is inherently non-sensitive to radioactive iodine. Hence, its management is more difficult and its prognosis is worse than DTC [7]. The overall survival rate is between 75 and 85% during 10 years for individuals with MTC [13]. In spite of aggressive surgical treatment, there is almost a 50% of chance for persistent or recurrent disease, with deleterious effects on quality of life and the reduced 10-year survival rate by 40% [7, 13].

Conclusion: Findings of the study revealed that in the absence of the established treatment for the patients with RR-DTC and metastatic MTC, PRRT could be effective with few adverse events.

Trial registration: PROSPERO registration number: CRD42019125245.

Keywords: Peptide receptor radionuclide therapy, Radioiodine refractory-differentiated thyroid Cancer, Medullary thyroid carcinoma, Papillary thyroid carcinoma, Yttrium-90, 177Lu-DOTATATE, Indium-111, Systematic review

Methods
Search strategy and selection criteria
A systematic review was performed on the published works to investigate safety and efficacy of PRRT in the patients with advanced RR-DTC and metastatic MTC, according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [18].

Eligibility criteria
All the original studies containing data related to PRRT were considered eligible to be included in the review study. Exclusion criteria were irrelevant papers (based on screening of titles and abstracts), papers with insufficient data available, duplications, and review papers. All the eligible studies were included to assess efficacy, and/or safety of PRRT.

Study identification
For this systematic review, the Cochrane Central Register of Controlled Trials (Central), Medline (PubMed, Ovid, and Ebsco), Scopus, and Embase databases were searched (from database inception to March 24, 2021). Search terms for English-language publications included: “peptide receptor radionuclide therapy”, “PRRT”, “radio-nuclide therapy”, “radiolabeled somatostatin analogues”, “thyroid cancer”, “thyroid carcinoma”, “thyroid neoplasm”, “differentiated thyroid cancer”, “differentiated thyroid carcinoma”, “differentiated thyroid neoplasm”, “medullary thyroid cancer”, “medullary thyroid...
carcinoma”, and “medullary thyroid neoplasm”. Details regarding the search strategy are provided in the Supplementary Table 1.

The first search was done independently by two investigators (ZE and ZM). Also, a complete updated search was performed on all databases available and new studies (if any exist) were identified to assess the details and incorporate findings in this review. The snowballing techniques were used to complete the search by screening reference lists of the included papers for relevant studies. Also, registry of prospective studies with accessible results was searched. Two authors (RM, ZM) independently determined studies that should be evaluated further by scanning the title, abstract, or both based on the inclusion/exclusion criteria, the reviewers were blinded to names of the journals and authors. All the potentially relevant papers as full texts were assessed and any disagreements were resolved by consensus or by arbitration of two experts (MK and MM). In case of duplicates or multiple publications of a primary study, yield of information was enhanced by collating all available data and using the most complete data set aggregated across all the known publications.

Data collection and management

Two reviewers (RM and ZM) independently extracted the data from the included trials and any disagreement was adjudicated by consensus or by arbitration of other reviewers (MK and MM). Published reports were obtained for every study, and standard information was extracted in a spreadsheet. The following data were extracted: author’s name; year of publication; country where the study was performed; number of participants, sex and age of the participants; tumor classification, site of metastases; prior treatments (cumulative radioiodine in RR-DTC); cumulative activity (GBq) of PRRT; response to treatment criteria; time to progression (TTP); follow-up duration; response to treatment; complications (major/minor); mortality rate; and time to death.

Biochemical response was defined in the patients with DTC based on serum thyroglobulin (Tg) level and in the patients with MTC, it was defined based on serum calcitonin and carcino- embryonic antigen (CEA) levels. Different criteria were used to evaluate radiological responses to treatment, namely world health organization (WHO) criteria, response evaluation criteria in solid tumors (RECAST) criteria, and southwest oncology group (SWOG) criteria [19]. Moreover, the European organization for research and treatment of cancer (EORTC) has classified metabolic response to treatment based on the maximum standardized uptake value (SUVmax) [20]. For further analysis, proportions of complete and partial radiologic response were integrated as “objective response”.

Occurrence of adverse events was evaluated using common terminology criteria for adverse events (CTCA E) [21]. Two reviewers (RM and ZM) independently assessed methodological quality of the included studies using the tool of systematic reviews [22], and any disagreement was resolved by consensus.

Results

Search on the literature led to identification of 2284 publications, of which 98 papers were reviewed in full text (Fig. 1. shows flow chart of literature search and paper selection). The risk of bias of the included studies was low (Supplementary Table 2). Inter-reviewer’s agreement was “excellent” for the selected papers (Cohen’s test $\kappa = 0.96$). Among 41 publications met the inclusion criteria, 12 papers were retrospective in terms of design; 19 papers were prospective studies and remaining 10 papers were case reports. Tables 1 and 2 summarize characteristics of the included studies assessing efficacy of PRRT in the patients with advanced RR-DTC, and metastatic MTC, respectively. Data regarding safety of PRRT are presented in Table 3. Cumulative activity of PRRT ranged between 0.925–83.2 GBq. For $^{90}$Y -based agent, most of the studies had used this agent with an administered activity ranging from 0.925 to 5.9 GBq per cycle usually up to 4 cycles. For 177Lu-DOTA-TATE, the administered activity rate was between 5.5–7.7 GBq per cycle usually up to 4 cycles. In terms of follow-up duration, in the patients with advanced RR-DTC, it was between 1 and 99 months after commencement of PRRT (median: 12 months). It was between 1 and 144 months (median: 17 months) in the patients with metastatic MTC. Death was recorded in 109 patients. Time to death varied from 1 to 63 months (median: 11 months). It should be noted that more than one criterion was used to evaluate efficacy of PRRT, and some patients did not complete their full course of treatment.

Efficacy of PRRT in RR-DTC

Overall, 157 patients with advanced RR-DTC were treated with PRRT. Based on biochemical response criteria, from 79 treated patients, 20 cases of partial response (PR), 22 cases of stable disease (SD), and 37 cases of persistent disease (PD) were determined. Out of 91 patients whose radiological response was assessed, 9 cases of PR, 39 cases of SD, and 43 cases of PD were recorded. Metabolic response was evaluated in 48 patients. Six cases of PR, 20 cases of SD, and 22 cases of PD were identified.

In 85 patients treated with $^{90}$Y -based agent; 44 patients were assessed based on biochemical response.
among whom 8 cases of PR, 14 cases of SD, and 22 cases of PD were observed. Seven cases of PR, 23 cases of SD, and 25 cases of PD were identified in 55 patients assessed based on radiological response. Moreover, 2 cases of PR, 5 cases of SD, and 4 cases of PD were reported in 11 patients assessed based on metabolic response.

In 26 patients treated with Lutetium-177-based agent, 10 cases of PR, and 11 cases of PD showed biochemical response. Considering 20 patients assessed for radiological response, 2 cases of PR, 9 cases of SD, and 9 cases of PD were reported. Out of 9 patients assessed for metabolic response, 1 case of PR, 4 cases of SD, and 4 cases of PD were identified.

Moreover, in 18 patients treated with Indium-111, biochemical response was assessed in 14 patients. Two patients with PR, 8 cases with SD, and 4 cases with PD were reported. Seven SD cases and 9 PD cases were recorded based on radiological response in 16 patients.

Among 157 patients with RR-DTC, biochemical and objective responses (partial and complete) were observed in 25.3 and 10.5% of the patients, respectively.

**Efficacy of PRRT in metastatic MTC**

In total, 220 patients with metastatic MTC were treated with PRRT. Based on biochemical response to the treatment in 145 patients, 7 cases of complete response (CR), 47 cases of PR, 20 cases of SD, and 71 cases of PD were recognized.

Radiologic response was evaluated among 134 patients. Four cases of CR, 9 cases of PR, 75 cases of SD, and 46 cases of PD were observed. Considering metabolic response among 46 patients, 7 cases of PR, 29 cases of SD, and 10 cases of PD were identified.

Sixty-nine patients were treated by 90Y-DOTATOC, 88 patients were treated with 177Lu-DOTA-TATE, and 12 patients were treated with 111_Indium-based agent. Type of treatment was unknown in other patients.

In 69 patients treated with 90Y-DOTATOC, 1 case of CR, 15 cases of PR, 4 cases of SD, and 35 cases of PD (based on biochemical response criteria in 55 patients) as well as 2 cases of CR, 21 cases of SD and 15 cases of PD (based on radiological response criteria in 38 patients) and 1 case of PR and 1 case of PD (based on metabolic response criteria in 2 patients) were reported. Out of 74 patients treated with 177Lu-DOTA-TATE, 5 cases of CR, 26 cases of PR, 14 cases of SD, and 29 cases of PD were observed based on biochemical response criteria. Moreover, 9 cases of PR, 50 cases of SD, and 26 cases of PD were achieved in 85 patients based on radiological response criteria. Furthermore, SD was found in 3 patients based on metabolic response criteria. In the patients treated with 111_Indium-based agent; 1 case of CR, 2 cases of SD, and 4 cases of PD (in 7 patients
Table 1: Efficacy of peptide receptor radionuclide therapy (PRRT) in patients with advanced RR-DTC

| Reference (Publish Year) | Country | N  | Sex | Age (year) | Tumor Classification | Site of metastasis | Prior treatments (Iodine cumulative activity GBq (med)) | Ligand (Radionuclide Chelator Peptide) | Cumulative activity (GBq) | Response criteria | TTP in SD (month) | Follow-Up duration median: (months) | Response |
|-------------------------|---------|----|-----|------------|----------------------|-------------------|------------------------------------------------|--------------------------------------|--------------------------------------|--------------------------|----------------------|-------------------|-------------------------------|----------|
| Czepczynski R et al. (2014) [15] | Poland | 6 | F/M | (9/2) | Median: 65 (47–81) | 3FTC, 3HCTC | B/Lu/M | TT/ND/EBR/RIT (3.1) | 90Y-DOTATOC | 3.7–14.8 | Biochemical NA | 21 (2–68) | 4PD, 3PR, 1SD | 1PD, 2SD, 1PR |
| Versari A et al. (2014) [23] | Italy | 11 | F/M | Median: 59 (19–78) | 5PTC, 10Xophilic, 3FTC, 2Insular | Li/B/Lu | TT/ND/RT (5.55–33.3 (12.95)) | 90Y-DOTATOC | 4.329–17.95 | Biochemical NA | 775 (35_11.5) | 11SD | 2PR, 4SD, 4PD, 1NA |
| Iten F et al. (2009) [24] | Switzerland | 24 | F/M | (12/12) | Median: 58.8 (40.5–80.6) | 17FTC, 5PTC, 2 No specified | NA | TT/ND/RT | 90Y-DOTATOC | 5.6–30.3 | Biochemical NA | 7.75 (3.5–99.1) | 17PD, 1PD |
| Gabriel M et al. (2004) [25] | Austria | 5 | F/M | (2/3) | Median: 59 (51–73) | 3FTC, 2PTC | B/Lu/M | TT/ND/RT (9.25_29.91 (18.87)) | 90Y-DOTATOC | 5.5_7.4 | NA | 5 | NA | 5SD |
| Gorges R et al. (2001) [26] | Germany | 3 | F/M | (2/1) | Median: 68 (51–72) | Papillary-oxyphilic, follicular-oxyphilic, 1Hürthle cell carcinoma | Li/B/Lu/M | TT/ND/EBR/RT | 90Y-DOTATOC | 1.7_4.96 | Biochemical NA | 20 (16_31) | 2SD, 1PD |
| Waldherr R et al. (2001) [27] | Switzerland | 7 | F/M | (4/3) | Median: 60 (44_74) | 4PTC, 3FTC | NA | TT/ND/EBR/RT/C/EN | 90Y-DOTATOC | 1.7_14.8 | WHO | 8 | 15 (1_31) | 2SD, 5PD |
| Vergolini I et al. (2002) [28] | UK | 25 | NA | NA | NA | NA | NA | NA | 90Y-DOTA-Lanerotide | 0.925_7.06 | WHO | 36 | 3PR, 11SD, 11PD |
| Traub-Weidinger T et al. (2011) [29] | Austria | 4 | NA | Median: 66 | 1FTC, 1HCTC | B/Lu | TT/ND/EBR/RT | 90Y-DOTATOC | 7.2_7.4 | Imaging NA | (22_27) | 4PD |
| Basu S et al. (2020) [30] | India | 8 | M/F | (5/3) | Median: 66 | 1FTC | B/Lu/M | TT/ND/RT | 177Lu-DOTATATE | 5.5_25.4 | Biochemical NA | 347_52 | 3PR, 2SD |
| Cinir, H. Y et al. (2020) [31] | Turkey | 4 | M/F | (3/1) | Median: 64 (49_67) | 1FTC, 3PTC | Lu/B | TT/ND/RT/C | 177Lu-DOTATATE | 148_241 | Imaging EORTC | 5.5 (1.7_9.4) | 1PD, 2SD, 1PR |
| Roll W et al. (2018) [32] | Germany | 5 | M/F | (4/1) | Median: 75 (62_89) | 3FTC, 1PTC, 1HCTC | NA | TT/ND/EBR/RT | 177Lu-DOTATATE | Mean: 7.0 ± 0.7 | Biochemical NA | 6 (3_9) | 1FTC PR, 4PD |
| Oliván-Sasot, P et al. (2017) [33] | Spain | 1 | F | 69 | FTC | B/Li | TT/ND/C/RT (10.4) | 177Lu-DOTATATE | 2.6 | Imaging NA | 6 | PR |
| Elboğa, U et al. (2016) [34] | Turkey | 1 | M | 64 | PTC (tall cell variant) | B/Lu/M | TT/ND/RT (27.75) | 177Lu-DOTATATE | 7.4 | Biochemical NA | After second cycle | PR |
| Reference (Publish Year) | Country | N  | Sex | Age (year) | Tumor Classification | Site of metastasis | Prior treatments (iodine cumulative activity GBq (med)) | Ligand (Radionuclide Chelator Peptide) | Cumulative activity (GBq) | Response criteria | TTP in SD (month) | Follow-Up duration median: (months) | Response |
|--------------------------|---------|----|-----|------------|----------------------|-------------------|----------------------------------|----------------------------------|-------------------------|----------------|----------------|-----------------------------|----------|
| Jois B et al. (2014) [35]| India   | 1  | NA  | NA         | PTC                  | NA                | TT/ND/EBR/RIT (NA)                | 177Lu-DOTATATE                  | 7.4                     | Biochemical Imaging       | NA             | 3              | PR                          | SD       |
| Teunissen JJ et al. (2005) [36]| Netherlands | 5  | F/M | Median: 52 (52_76) | 3HTC, 1FTC, 1PTC | B/Lu             | TT/ND/EBR/C/RIT (15.1_16.7 (12.9)) | 177Lu-DOTATATE             | 22.4-30.1             | Biochemical WHO          | Median: 22(4-63) | (4-48) | 2PD, 3PR, 5SD, 1PD, 1PR, 1MRe |
| Parihar AS et al. (2018) [37]| India   | 1  | F   | 54        | PTC                  | B/Lu             | TT/ND/RT (18.5)                  | 177Lu-DOTA- RGD2              | 5.5                    | REOST             | NA             | 4              | PR                          | SD       |
| Campenni A et al. (2015) [38]| Italy   | 1  | M   | 70        | PTC                  | Lu               | TT/ND/RT (3.7)                   | 177Lu-DOTATOC                | 7.77                   | REOST             | 5              | PR                          | SD       |
| Valkema R et al. (2002) [39]| Netherlands | 5 | NA  | Median: 70.8 (57.3_76.1) | 4PTC, 1FTC | Lu               | TT/ND/BR/RT                     | 1111In-Octreotide          | 29.5_83.2          | Biochemical SWOG        | 15.8 (13.2_28.2) | 15D, 1PD, 1PR, 2NA | 4PD                        | SD       |
| Krenning E et al. (1999) [40]| Netherlands | 1 | NA  | NA         | PTC                  | NA               | NA                              | 1111In-Octreotide          | 20_75                  | imaging            | NA             | 24             | 1SD                        | 1SD      |
| Stokkel MP et al. (2004) [41]| Netherlands | 11 | F/M | Median:67 (44-69) | 6PTC, 5FTC | Lu/Lu/M            | TT/ND/EBR/Emb/RT              | 1111In-DTPA-Octreotide     | 143_33.1             | Biochemical Imaging     | 12 (1_12) | 7SD, 3PD, 1NA | 4SD, 5PD, 2NA           | 4SD, 5PD, 2NA |
| Budilawan H et al. (2013) [42]| Germany | 7  | F/M | Median: 64.5 (56_77) | 4FTC,3HCTC | A/Lu/Lu/B | TT/ND/EBR/C/RIT/ UTT/REDIFF  | 90Y-DOTATATE and 177Lu-DOTATATE | NA | EORTC             | NA             | 50.4 (34.8-69) | 15D, 5PD, 2NA | 1PR                        | 5PD, 10SD |
| Scalorbi F et al. (2017) [43]| Italy   | 21 | F/M | Median:13 (8) | NA                  | NA               | TT/ND/RT                        | NA                              | NA | EORTC             | NA             | 2PR, 5PD, 10SD | 5PD, 10SD | 2PR, 5PD, 10SD |

Abbreviations: NA Not Available, FTC Follicular Thyroid Carcinoma, RR-DTC Radioiodine-Refactory Differentiated Thyroid Cancer, PTC Papillary Thyroid Carcinoma, HCTC Hurtle Cell Thyroid Carcinoma, TTP Time To Progression
Metastatic Site: A Adrenal, L Liver, Lu Lung, B Bone, M Mediastinum
Prior treatments: TT Total Thyroidectomy, ND Node Dissection, EBR External Beam Radiation, C Chemotherapy, I Radioactive Iodine therapy, BT Biotherapy with octreotide, UTT Laser- induced thermotherapy, REDIFF Redifferentiation Using Roaccutane
Response: CR Complete Response, PR Partial Remission, SD Stable Disease, PD Progressive Disease, MR Minor Remission
Table 2 Efficacy of peptide receptor radionuclide therapy in patients with metastatic MTC

| Reference (Publish Year) | Country     | N | Sex  | Age  | Site of metastasis | Prior treatment | Ligand (Radionuclide Chelator Peptide) | Cumulative activity (GBq) | Response criteria | TTP in SD (month) | Follow-Up duration (months) | Response |
|-------------------------|-------------|---|------|------|--------------------|-----------------|----------------------------------------|--------------------------|------------------|-----------------------------|------------------------|----------|
| Öksüz M et al. (2014)  | Switzerland | 1 | NA   | NA   | NA                 | TT/N/D/C        | 90Y-DOTA-TOC                          | 5.65                     | Biochemical      | NA             | 3                       | PD                     |
| Bertagna F et al. (2009)| USA         | 1 | M    | 74   | B/M               | TT/N/D/RF       | 90Y-DOTA-TOC                          | 9.01                     | Biochemical      | NA             | 7                       | SD                     |
| Iten F et al. (2007)   | Switzerland | 31| F/M  | Mean: 56.7 (240–76.9) | NA             | TT/N/D/C/E/B  | 90Y-DOTA-TOC                          | 1.7–29.6                 | Biochemical      | NA             | 15.7 (1.4–107)  | 9R, 22NR               |
| Bodei L et al. (2004)  | Italy       | 21| F/M  | Median: 53 (31–78) | Lu/L/V/B/M      | TT/N/D/C/E/B/T | 90Y-DOTA-TOC                          | 7.5–19.2                 | Biochemical      | NA             | 40                      | 3SD, 12PD, 5PR, 1CR       |
| Gao ZR et al. (2004)   | China       | 1 | M    | 58   | Lu/ M             | NA              | 90Y-DOTA-TOC                          | 3.33                     | Biochemical      | 6              | 10.5                    | PR                     |
| Waldherr C et al. (2001)| Switzerland | 12| F/M  | Median: 60 (24–72) | NA              | TT/N/D/C/E/B/T/EN | 90Y-DOTA-TOC                          | 1.7–14.8                 | WHO             | 10 (3–14)      | 15 (1–31)               | 5SD, 7PD               |
| Otte A et al. (1999)   | Switzerland | 2 | F    | 65   | NA                | NA              | 90Y-DOTA-TOC                          | 9.25–9.62                | WHO             | NA             | 24                       | 2SD                   |
| Bilgic, S et al. (2020)| Turkey      | 19| F/M  | 32–87 | Lu/L/V/B/M        | TT/N/D/C         | 177Lu-DOTATATE                        | 6.5–52.3                 | Biochemical      | NA             | NA                      | 7SD, 8PR, 4PD          |
| Cinkir, H. Y et al. (2020)| Turkey    | 3 | M    | Median: 53 (38–59) | Lu/B/M          | TT/N/D/C/E/B  | 177Lu-DOTATATE                        | 14.8–44.4                | EORTC           | 37.3 (17.6–56.9)| 24.2 (10.48)           | 3SD                   |
| Parghane, R. V et al. (2020)| India   | 43| F/M  | Median: 48 (25–80) | Lu/L/V/B/M      | TT/N/D/C/E/B  | 177Lu-DOTATATE                        | 5.55–33.3                | Biochemical      | 24 (15.1–32.9) | 26 (16.6–35.3)          | 5CR, 4SD, 13PR, 21PD   |
| Makis W et al. (2015)  | Canada      | 1 | NA   | Median: 56.5 (38.75) | B/M             | TT/N/D         | 177Lu-DOTATATE                        | 22.2                     | Biochemical      | 9.5 (9–10)    | 1PR, 1PD                | 2SD                   |
| Vaisman F et al. (2015) | Brazil      | 7 | NA   | Median: 35.8 (20–54) | NA              | NA            | 177Lu-DOTATATE                        | 29.6                     | REOST            | NA             | 12                      | 3PR, 3SD, 1PD           |
| Soydal Ç et al. (2014) | Turkey      | 2 | F/M  | Median: 41 | Lu/Li            | TT/N/D/E/B/R  | 177Lu-DOTATATE                        | 29.6                     | REOST            | NA             | 6 weeks After fourth cycle | 2SD                   |
| Beukhof, C et al.      | Netherlands | 10| F/M  | Median: 62 | NA              | NA            | 177Lu-octreotide                      | 27.8–29.6                | Biochemical      | 8.4 (3.6–)  | 16.88 (4.8–144)        | 3SD, 4PR,               |
| Reference (Publish Year) | Country | N | Sex | Age | Site of metastasis | Prior treatment | Ligand (Radionuclide Chelator Peptide) | Cumulative activity (GBq) | Response criteria | TTP in SD (month) | Follow-Up duration (months) | Response |
|--------------------------|---------|---|-----|-----|-------------------|----------------|-------------------------------------|-------------------------|-----------------|-------------------|---------------------------|----------|
| (2019) [54]              |         | 64 |     | (19-75) |                  |                |                                     |                         |                 | 144               | 3PD                       | 4SD, 6PD  |
| Mathew, D et al. (2018)  | India   | 2  | NA  | NA  | NA                | NA             | 177Lu-octreotide                  | NA                     | RECIST          | Imaging           | 7 weeks After last cycle | 2SD      |
| Pasieka JL et al. (2004) | Canada | 1  | M   | 46  | M                 | TT/ND/C        | 1111n-Octreotide                  | 11.954                  | Biochemical     | NA                | 9                        | PD       |
| Valkema R et al. (2002)  | Netherlands | 5 | NA  | Median: 57.4 (27.7-77.4) | B/Lu          | TT/ND/C/EBR/BT                  | 1111n-Octreotide    | 25.14-87.28    | Biochemical     | NA                | 7.8 (2.76-26.8)        | 2SD, 3PD  |
| Caplin M et al. (2000)   | Poland  | 1  | F   | 46  | NA                | NA             | 1111n-Octreotide                  | 11.4                    | Biochemical     | NA                | 24                       | 1SD, 2PD  |
| Krenning E et al. (1999) | Netherlands | 3 | NA  | NA  | NA                | NA             | 1111n-Octreotide                  | NA                     | Imaging         | NA                | 27.5 (22,33)           | 2CR      |
| Buscombe JR et al. (2003)| UK      | 2  | NA  | Median: 52 (46-58) | NA            | NA                            | 1111n-pentetreotide | 25.75          | RECIST          | NA                | 6PR, 3PD                |          |
| Hayes AR et al. (2019)   | UK      | 9  | NA  | NA  | NA                | NA             | 90Y-DOTATATE and/or 177Lu-DOTATATE | NA                     | Biochemical     | 14 (8-20)       | NA                | 17SD                    | 5PR      |
| Puranik A et al. (2019)  | India   | 28 | F/M | 14/14 | Mean: 479 (26-72) | NA             | TT/ND/C/EBR                      | 90Y-DOTATATE and 177Lu-DOTATATE | NA             | EORTC             | 36                       | 5PD      |
| Budlawn H et al. (2013)  | Germany | 7  | F/M | 3/4 | Median: 66.5 (21-68) | Lu/Li/B        | TT/ND/EBR/177Lu-DOTATATE         | NA                     | EORTC           | NA                | 50.4 (34.8-66)         | 4SD, 1PD, 1PR |
| Scalorbi F et al. (2017) | Italy   | 7  | F/M | 4/3 | NA                | NA             | NA                                  | NA                     | NA             | NA                | 24                       | SSD, 2PD  |

Abbreviations: NA Not Available, MTC Medullary Thyroid Carcinoma, TTP Time To Progression
Metastatic Site: A Adrenal, L Liver, Lu Lung, B Bone, M Mediastinum
Prior treatments: TT Total Thyroidectomy, ND Node Dissection, EBR External Beam Radiation, C Chemotherapy, BT Biotherapy with Octreotide, LITT Laser Induced Thermotherapy, REDIFF Redifferentiation Using Roaccutane
Response: CR Complete Response, PR Partial Remission, SD Stable Disease, PD Progressive Disease, MR Minor Remission
| Reference                     | Kind of PRRT               | Number & Kind of Tumor  | Cumulative activity (GBq) | Hematologic Toxicity | Gastrointestinal & Hepatobiliary Toxicity | Genitourinary Toxicity | Others | Mortality (Median time to death since the first course of PRRT (months)) |
|-------------------------------|----------------------------|-------------------------|---------------------------|----------------------|------------------------------------------|------------------------|--------|---------------------------------------------------------------------|
| Bertagna F et al. [44]        | 90Y-DOTATOC                | 1MTC                    | 9.01                      | None                 | None                                     | None                   | None   | 1 (NA)                                                              |
| Bodei L et al. [46]           | 90Y-DOTATOC                | 21MTC                   | 7.5–19.2                  | 15                   | NA                                       | None                   | NA     | 4 (NA)                                                              |
| Bodei L et al. [61]           | 90Y-DOTATOC                | 4MTC                    | 3.8_19.2                  | None                 | None                                     | None                   | None   | None                                                                |
| Czepczynski R et al. [15]     | 90Y-DOTATOC                | 3FTC, 3HCTC             | 3.7_14.8                  | 6                    | None                                     | None                   | None   | 1 (63)                                                              |
| Gorges R et al. [26]          | 90Y-DOTATOC                | 1papillary-oxiphilic, 1follicular-oxiphilic, 1Hurthle cell carcinoma | 3mild Lymphocytopenia  | None                 | None                                     | None                   | None   | 1 (16)                                                              |
| Iten F et al. [24]            | 90Y-DOTATOC                | 17FTC, 5PTC, 2No specified | 5.6–30.3                 | 3Anemia, 3Transient Thrombocytopenia, 1Transient Leukopenia | 4nausea                   | 4permanent renal toxicity | None   | 11FTC, 4PTC, 2No (13.7)                                               |
| Iten F et al. [45]            | 90Y-DOTATOC                | 31MTC                   | 74.5                      | 3Transient Leukopenia, 1Transient Thrombocytopenia | 5Nausea                   | 6                   | NA                      | 22 (25.8)                                             |
| Versari A et al. [23]         | 90Y-DOTATOC                | 5PTC, 1Oxiphilic, 3FTC, 2Insular | 4.329_17.95              | 2Transient Anemia, 2Transient Leukopenia | 4nausea, 1transient increase of transaminase | 1permanent renal toxicity | 2Asthenia | None                                                                  |
| Waldherr C et al. [27]        | 90Y-DOTATOC                | 12MTC, 4PTC, 3FTC        | 1.7_14                    | 6Anemia, 10Transient Lymphocytopenia | NA                       | NA                   | NA                      | 1 (1)                                                              |
| Traub-Weidinger T et al. [29]  | 90Y-DOTA-Lanerotide       | 1FTC, 1PTC              | 7.2_7.4                   | None                 | None                                     | 1renal toxicity        | None   | 1 (22)                                                              |
| Basu. S et al. [30]           | 177Lu-DOTATATE             | 8 DTC                   | 5.5_25.4                  | None                 | None                                     | 1transient             | None   | 2 (4_12)                                                             |
| Beukhof, C et al. [54]        | 177Lu-Octreotate           | 10MTC                   | None                      | 1Diarrhea            | None                                     | 1Hemoptysis            | 7MTC, 1another cause |                                                                      |
| Cinkir, H. Y et al. [31]      | 177Lu-DOTATATE             | 3MTC, 3PTC, 1FTC        | 14.8_44.4                 | 2Transient Anemia, 3Transient Leukopenia | None                   | None                  | None                   | 1MTC, 2PTC                                                             |
| Parghane, R. V et al. [50]    | 177Lu-DOTATATE             | 43MTC                   | 5.55_33.3                 | 1Transient           | 1Nausea                                 | None                   | None   | 20                                                                   |
| Teunissen j et al. [12]       | 177Lu-DOTATATE             | 3HCTC, 1FTC, 1PTC       | 22.4–30.1                 | NA                   | NA                                      | NA                     | NA       | 1 (48), 1 (4)                                                       |
| Vaisman F et al. [52]         | 177Lu-DOTATATE             | 7MTC                    | NA                        | NA                   | NA                                      | NA                     | NA       | 1transient sexual dysfunction, 2mild hair Loss, 1hypersensitivt dermatologic lesions | 2 (1/7 before the end of the protocol) |
| Valkema R                     | 5MTC, 5DTC                 | NA                      | None                      | None                 | None                                     | None                   | None   | 4MTC (11.22)                                                        |
assessed based on biochemical response) and also, 2 cases of CR, 4 cases of SD, and 5 cases of PD (in 11 patients assessed based on radiological criteria) were reported.

Overall, in the patients with metastatic MTC, biochemical and objective responses were observed in 37.2 and 10.6% of the patients, respectively.

Safety of PRRT
Safety of PRRT was assessed in 19 studies (totally, 239 patients). Death was observed in 109 patients. In addition, time to death varied from 1 to 63 months. In 95 patients with advanced RR-DTC, 46 patients died. Time to death ranged from 1 to 63 months from commencement of PRRT. Based on type of PRRT, death occurred in 29/55 patients treated with 90Y-based agent, 6/17 patients treated with 177Lu-DOTA-TATE, and 8/16 patients treated with 111In-Octreotide. Among 44 patients with metastatic MTC, 63 patients died. Time to death ranged from 1 to 26.8 months since initiating the first course of PRRT. Based on type of PRRT, death occurred in 27/69 patients treated with 90Y-DOTATOC, 31/63 patients treated with 177Lu-DOTA-TATE, and 4/5 patients treated with 111In-Octreotide. Major side effects were reported in 124 patients treated with 90Y-based agent. Fourteen patients developed renal toxicity (2 cases of grade 4, 2 cases of grade 3, 2 cases of grade 2, and 8 cases of grade 1). Furthermore, hematologic toxicity was observed in 64 patients (3 cases developed grade 4 of thrombocytopenia, and 1 patient reported to suffer from grade 4 of anemia). Moreover, in 80 patients treated with 177Lu-DOTA-TATE, mild and transient hematologic and renal complications were reported (4 patients with grade 1 and one case with grade 2 of hematologic toxicity and one patient with grade 2 of renal toxicity). Among 21 patients treated with 111In-Octreotide, one patient developed transient thrombocytopenia (grade 1).

**Discussion**

Herein, a comprehensive systematic review was done to investigate efficacy and safety of PRRT in management of advanced RR-DTC and metastatic MTC. The results suggested that PRRT could maintain disease stability with few adverse events. In short-term, toxicity is mild and transient. In addition, long-term toxicity is rare and with low grade. To the best of our knowledge, no similar systematic review or meta-analysis has been done previously to investigate efficacy and safety of PRRT in RR-DTC and metastatic MTC.

There are few recommended treatments for the patients with RR-DTC and therapeutic options are associated with certain limitations in case of the patients with metastatic DTC. The choice of treatment depends on bulk of the tumor. Simple observation, multi-targeted, or mutation-selected kinase inhibitors (MKI), and traditional cytotoxic chemotherapy are the available options [12, 62]. Despite approval of doxorubicin by the food and drug administration (FDA), treatment with cytotoxic agents has shown disappointing results [63]. Therefore, benefit-risk ratio must be carefully evaluated before starting treatment [62].

For majority of the patients with MTC, primary surgery is curative at early stages. However, local and distant metastases after surgery are the major causes of mortality [14]. Resurgery, chemotherapy, external beam radiation therapy, and biological agents, such as RET and MEK inhibitors have yielded disappointing and limited results. Although, treatment with tyrosine kinase inhibitors (TKIs) (Vandetanib and Cabozantinib) improves progression-free survival (PFS), severe adverse events could limit the use of them. There is no curative

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**Table 3 Safety of Peptide Receptor Radionuclide Therapy in patients with Advanced RR-DTC & Metastatic MTC** (Continued)

| Reference | Kind of PRRT | Number & Kind of Tumor | Cumulative activity (GBq) | Hematologic Toxicity | Gastrointestinal & Hepatobiliary Toxicity | Genitourinary Toxicity | Others | Mortality (Median time to death since the first course of PRRT (months)) |
|-----------|--------------|------------------------|--------------------------|---------------------|------------------------------------------|-----------------------|--------|---------------------------------------------------------------------|
| et al. [39] | Octreotide | 16PTC, 4FTC | 14.3, 33.1 | Thrombocytopenia | None | None | None | 1 (5), 2 non related (1, 3) |
| Stokkel Mp et al. [41] | 111In-DTPA-Octreotide | 6PTC, SFTC | 14.3, 33.1 | Thrombocytopenia | None | None | None | 1 (5), 2 non related (1, 3) |
| Budiawan H et al. [6] | 90Y-DOTATATE and 177Lu-DOTATATE | 7MTC, 4FTC, 3HCTC | NA | 8 minor hematologic, 5Anemia, 1Leukopenia | 6 transient increase of transaminase | 5 mild renal toxicity | None | 1 MTC (12), 2FTC (12), 1HCTC (24) |

Abbreviations: Na Not Available, RR-DTC Radioiodine-Refractory Differentiated Thyroid Cancer, FTC Follicular Thyroid Carcinoma, PTC Papillary Thyroid Carcinoma, HCTC Hurte Cell Thyroid Carcinoma, MTC Medullary Thyroid Carcinoma
treatment for these patients, and all the available treatment modalities have been shown to have certain limitations and complications [6].

In the 1990s, the role of SSTR in regulation and proliferation of normal thyroid cells and tumoral tissues was reported that led to introduction of peptide receptor imaging and PRRT in management of metastatic MTC and advanced RR-DTC [15]. Type of SSTRs expression could have an effect on survival rate of these patients [64]. From 5 subtypes of SSTR described in human cells, SSRT2 is expressed in MTC [7]. However, SSRT2 expression has not been identified in papillary or follicular thyroid cancer, and it is irregularly expressed in Hurthle cell adenoma and Hurthle cell carcinoma [65].

Generally, PRRT is able to deliver a high dose of radiation to intracellular components of cancer cells, and induce tumor shrinkage [7]. Currently, PRRT is considered as a safe and effective treatment modality for metastatic inoperable well-differentiated neuroendocrine tumors and advanced pheochromocytomas and paragangliomas [16, 17].

The most frequently used radionuclides in PRRT are 90Y and Lutetium-177. They have different physical characteristics, namely different emission ranges. This results in various maximum tissue penetrations ranging from 3 mm for Lutetium-177 to 12 mm for 90Y. Since, 90Y has the highest energy and maximum tissue penetration; it is a preferable radionuclide for tumors with large size and poor vascularization. On the other hand, Lutetium-177 emits intermediate-energy suitable for small-sized tumors. Few studies have used 111In-Octreotide, with tissue penetration ranging from 0.2 to 10 mm (Table 1) [7]. Krenning et al., for the first time reported treatment of the patients with advanced DTC with 111In-Octreotide analogs. One patient, who received total cumulative activity of at least 20 GBq showed disease stabilization [40]. In a pilot study conducted in Netherlands, 9 patients with advanced RR-DTC were treated with high, fixed doses of 111In-Octreotide. Six months after the last therapy, 4 patients had SD, and 5 patients showed PD. Mean Tg value was higher in PD cases than patients with SD. They concluded low Tg value could have a positive effect on the outcome [41].

Görges et al., in a study regarding the first cases of treatment with 90Y-DOTATOC in 3 patients with advanced RR-DTC and pulmonary metastasis showed deceleration in short-term disease progression [26]. In the last report on treatment with 90Y-DOTATOC in RR-DTC, median survival was found to be 21 months from initiating the first course of PRRT with only minor and transient hematological toxicity in some patients [15]. Recently, 177Lu-DOTA-TATE has been used more than 90Y but, number of patients treated with this somatostatin analog was limited.

In the patients with metastatic MTC, limited experience with PRRT treatment has been reported. Results of a study on the patients with metastatic MTC suggested that treatment with 90Y-DOTATOC is associated with a long-term survival benefit. However, treatment response was independent of pre-treatment scintigraphy results [45]. Recently, Beukhof et al., reported 17 years of experiences with 177Lu-octreotate treatment. They concluded that this treatment could be considered as a treatment in the patients with high uptake on 111In-DTPA-Octreotide scan (uptake grade 3) and positive SSTR2a expression in tumor histology [54]. Budiawan et al., found that the patients with RR-DTC having good response had less undergone other treatment modalities prior to PRRT than non-responders. In addition, they introduced lung metastasis as a poor prognostic factor for survival after PRRT [6].

However, PRRT is not free from adverse effects and minor complications,such as nausea, asthenia, and elevation in liver enzyme level are observed in up to 16.7% of patients, while major complications,such as nephrotoxicity and hematologic adverse events are rare and transient [23, 24]. Proximal tubular reabsorption of radio peptide and its interstitial retention lead to glomerular fibrosis [40], which is markedly observed after treatment with 90Y-DOTATOC. Hence, kidney protection is mandatory along with co-administration of positively-charged amino acids,such as L-lysine and/or L-arginine competitively inhibiting proximal tubular reabsorption of the radio peptide, or prolonged infusion over 10 h to 2 days after administration of radio peptide. Despite kidney protection, loss of renal function may become clinically evident years after PRRT, especially after administration of 90Y-DOTATOC. Sporadic reported cases of delayed renal failure have received activities greater than 7.4 GBq /m2 in very few cycles, without kidney protection [61]. Cumulative and per-cycle renal uptake dose, age, hypertension, diabetes and previous chemotherapy with nephrotoxic agents could accelerate the decrease in renal function after PRRT [66]. Considering these risk factors, one can modify treatment plan or change choice of radio peptide based on burden of tumors. Hematologic side effects generally are mild and temporary,such as reduction in count of lymphocytes and platelets [57].

Our systematic review demonstrated that treatment with PRRT not only could lead to minor complications in approximately 10% of cases but also it can cause very rare and transient major complications.

This systematic review benefited from a comprehensive search conducted by two independent investigators, no time limits, independent reviews by two reviewers,
and no publication bias. However, the main limitation of the present study was low quality of the available evidence. However, other underlying problems and limitations included retrospective nature of the studies, a selection bias, the amount of radioactivity administered (1–83 GBq), non-uniform response criteria, huge difference in follow-up periods (1–99 months), and the limited number of patients per report. Also, our search was restricted to English-language papers.

This systematic review investigated efficacy and safety of PRRT in treatment of RR-DTC and metastatic MTC. Given paucity of evidence, it is recommended to perform further multi-center randomized controlled clinical trials.

Conclusions
According to findings of our study, due to lack of various treatment modalities, PRRT could be an option for treatment of advanced RR-DTC, as well as metastatic MTC, with few adverse events.

Abbreviations
RR-DTC: Radioiodine-refractory differentiated thyroid cancer; MTC: Medullary thyroid cancer; PFS: Progression-free survival; SSTTR: Somatostatin receptor; PRRT: Peptide receptor radionuclide therapy; TTP: Time to progression; Tg: Thyroglobulin; CEA: Carcino embryogenic antigen; WHO: World health organization; RECIST: Response evaluation criteria in solid tumors; Tg: Thyroglobulin; CEA: Carcino embryogenic antigen; WHO: World health organization; PFS: Progression-free survival; SSTR: Somatostatin receptor; RR-DTC: Radioiodine-refractory differentiated thyroid cancer; MTC: Medullary thyroid cancer; FDA: Food and drug administration.

Supplementary Information
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Additional file 1: Supplemental Table 1. Medline (Pubmed, Ovid and Embase), Scopus, Embase, Web of Science and the Cochrane Library database (Last Updated March 24, 2021).

Additional file 2: Supplemental Table 2. Risk of bias assessment.

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MK had the original idea of this work. MK, MM, RM and ZM designed and performed the data extraction and wrote the manuscript. All authors critically revised the draft of the manuscript and approved its final version.

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