

Original Article

Clinical efficacy of ^{177}Lu -DOTATATE peptide receptor radionuclide therapy in thyroglobulin-elevated negative iodine scintigraphy: A “not-so-promising” result compared to GEP-NETs

ABSTRACT

This study aimed at assessing the performance of ^{177}Lu -DOTATATE-based peptide receptor radionuclide therapy (PRRT) in de-differentiated thyroid carcinoma thyroglobulin-elevated negative iodine scintigraphy (TENIS) in terms of clinical efficacy and outcome. This is a retrospective analysis of patients of TENIS who had undergone PRRT in a tertiary care setting. The selected patients were analyzed for the following parameters: (i) the patient characteristics, (ii) the metastatic burden, (iii) study of PRRT cycles and activity, (iv) response assessment (undertaken by three-parameter scale: symptomatic including Karnofsky/Lansky Performance scoring, biochemical and scan features) employing predefined criteria (detailed in methods), and (v) Grade III/IV hematological or renal toxicity. According to the qualitative uptake of the tracer in somatostatin receptor (SSTR)-based imaging (with either $^{99\text{m}}\text{Tc}$ -HYNIC-TOC/ ^{68}Ga -DOTATATE), the lesions were divided into the following four categories: Grade 0: no uptake, Grade I: uptake less than the liver but more than background, Grade II: uptake equal to the liver, and Grade III: uptake more than the liver. A total of eight patients of TENIS who had undergone ^{177}Lu -DOTATATE were retrieved. Among those eight patients, the follow-up duration (from the time of the 1st PRRT cycle) at the time of analysis ranged from 7 to 52 months, with an average of 34 months. At the time of assessment, two (25%) out of the eight patients had expired due to extensive metastatic disease and 6 (75%) were alive. On symptomatic response, complete disappearance of symptoms was found in one patient (12.5%), whereas three patients (37.5%) showed partial improvement in symptoms after PRRT and four patients (50%) showed worsening of and appearance of new symptoms. On biochemical response, reduction in serum thyroglobulin (TG) was found in three patients (37.5%) after PRRT and increase in serum TG was noticed in the rest of five patients (62.5%). Imaging response showed stable scan in two patients (25%) and progressive disease (PD) in six patients (75%), following a progression-free survival ranging from 7 to 16 months, when they were considered for tyrosine kinase inhibitors in view of PD. There was no obvious evidence of Grade III/IV hematological or renal toxicity in any of the patients, suggesting that the therapy in this group of patients is well tolerated. In addition, we also observed that most patients of TENIS showed low-grade uptake on SSTR-based imaging (Grade II as per our semi-quantitative scale), with only one patient showing Grade III uptake. ^{177}Lu -DOTATATE PRRT demonstrates modest response in SSTR-positive metastatic TENIS patients: (i) low SSTR expression and tracer avidity, and correspondingly lesser degree of targeting by the therapeutic agent and (ii) the fact that most of the TENIS patients usually have fluorodeoxyglucose (FDG)-avid disease, where high FDG avidity is commensurate with aggressive biology and could be the reason for the relatively less response documented. Larger prospective data need to be accrued in this domain in view of its well tolerability and nonavailability of better efficacious and less toxic treatment at present; however, this needs to be tried in receptor-positive cases with high-grade uptake (Score III/IV) for a definitive conclusion.

Keywords: ^{177}Lu -DOTATATE, peptide receptor radionuclide therapy, thyroglobulin-elevated negative iodine scintigraphy

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INTRODUCTION

With the evolution and wider availability of ^{177}Lu -DOTATATE, peptide receptor radionuclide therapy (PRRT) has gained popularity in the treatment of metastatic/advanced neuroendocrine tumors (NETs) over recent years.^[1,2] Most of the peer-reviewed literature and clinical application of this therapeutic modality (with either ^{177}Lu or with ^{90}Y labeled somatostatin analogs) have been on metastatic gastroenteropancreatic (GEP) NETs, where now it has an established role in Grade I and Grade II diseases, with substantially better health-related quality of life, symptomatic improvement, and disease stabilization.^[3-14] Therapeutic applications of PRRT beyond NET have been postulated to be possible in de-differentiated thyroid carcinoma, especially thyroglobulin-elevated negative iodine scintigraphy (TENIS) form. To date, there is paucity of reported literature on this subject across active treatment PRRT centers. Reservations exist with respect to the efficacy in this group which clearly behaves distinctly compared to the traditional classical indication of GEP-NET. There have been very few reports that have specifically looked into this group of thyroid cancer.^[15-17] Most of these studies conclude the requirement of further research; hence, analysis of PRRT performance, in terms of efficacy and outcome profile, both in prospective and retrospective settings, is a clear need for defining the appropriate role of this therapeutic approach in this clinical setting.

MATERIALS AND METHODS

This was a retrospective analysis of patients of metastatic TENIS who had undergone PRRT with ^{177}Lu -DOTATATE at a large tertiary care center. The pretreatment work-up and therapeutic protocol followed for these patients were according to our standard procedure similar with metastatic GEP-NETs,^[18] and included pretreatment somatostatin receptor (SSTR)-targeted imaging, renal and hematological parameter evaluation to determine the patient's suitability. Before undertaking the ^{177}Lu -DOTATATE PRRT, informed verbal and written consent was obtained from all patients selected for such therapy, which was based on discussion with the patients and relatives with respect to this treatment option versus tyrosine kinase inhibitor (TKI)-based treatment. The patients selected for the study fulfilled the following criterion: patients of metastatic TENIS who demonstrated uptake in the metastatic lesions on initial diagnostic study (^{68}Ga -DOTANOC/TATE or the $^{99\text{m}}\text{Tc}$ -HYNIC-TOC) and had received at least one cycle of PRRT with ^{177}Lu -DOTATATE. The selected patients were analyzed under the following parameters: (i) the

patient characteristics, (ii) the metastatic burden, (iii) study of PRRT cycles and activity and other treatment administered, (iv) response (using a three-parameter assessment: symptomatic including Karnofsky/Lansky Performance scoring and biochemical and scan features), and (v) any incidence of Grade III/IV hematological or renal toxicity in any of the patients. According to the qualitative uptake of the tracer in SSTR-based imaging (with either $^{99\text{m}}\text{Tc}$ -HYNIC-TOC/ ^{68}Ga -DOTATATE), the lesions were divided into the following four categories: Grade 0: no uptake, Grade I: uptake less than the liver but more than background, Grade II: uptake equal to the liver, and Grade III: uptake more than the liver.

Response evaluation

Response was assessed post-PRRT under the following three headings – clinical/symptomatic response (subjective response), biochemical response (tumor marker serum thyroglobulin [TG]), and radiological/molecular imaging response (^{18}F -fluorodeoxyglucose [FDG] positron emission tomography [PET]/computed tomography [CT] and SSTR imaging).

Response scales and definition of categories

Symptomatic response evaluation

An improvement in tumor-related symptoms based on the patient's subjective report relative to baseline symptoms was defined as symptomatic response. The patients were asked at follow-up with direct questioning on a scale of 0%–100% as to whether tumor-related symptoms had “disappeared:” 100% improvement (complete response [CR]), or “improved:” 30%–75% improvement (partial response [PR]), or were “stable:” <30% improvement (stable disease [SD]), or “worse:” >30% increase in symptoms or new symptoms of PD compared to baseline.

Biochemical response evaluation

Biochemical response was assessed by the serum TG levels. The baseline values of these biochemical markers before the start of PRRT were measured, and the percentage change after each cycle of PRRT was analyzed. More than a 75% reduction in biochemical marker was considered as CR, 30%–75% reduction as PR, <30% reduction or <30% increase as SD, and >30% increase in biochemical marker as PD.

Objective scan response evaluation: Anatomical imaging and molecular imaging

The Response Evaluation Criteria in Solid Tumor (RECIST 1.1) was used to evaluate anatomical imaging response in these TENIS cases. Molecular imaging response evaluation was undertaken by using PET-CT scan (^{68}Ga -DOTATATE and ^{18}F -FDG) with help of PET Response Criteria in Solid Tumors

(PERCIST), and molecular imaging responses were categorized into responders (CR, PR and SD) and non-responders (PD). The response evaluation scans were undertaken before each cycle of PRRT.

RESULTS

A total of eight patients of TENIS were retrieved after analyzing the records of thyroid cancer patients who had undergone PRRT. Out of the eight TENIS patients (male: female = 5:3, age range: 57–83 years), three patients had undergone one cycle of PRRT, two patients had undergone two cycles, another two patients had undergone four cycles of PRRT, and one patient received three cycles of PRRT. The histopathology included classical papillary Carcinoma of thyroid (PCT) ($n = 4$), follicular variant of PCT ($n = 2$), poorly differentiated carcinoma ($n = 1$), and follicular carcinoma thyroid ($n = 1$). The sites of metastases, the metastatic burden, and the grade of uptake on SSTR-based imaging are detailed in Table 1.

The sites of metastases and primary histopathology in the patients of TENIS are summarized in Table 2.

Somatostatin receptor/fluorodeoxyglucose dual-tracer imaging characteristics

The dual-tracer imaging characteristics (with SSTR and FDG) are elaborated in Table 3.

The follow-up duration (from the time of the 1st PRRT cycle) at the time of analysis ranged from 7 to 52 months. The number of cycles along with administered activity and duration of follow-up are summarized in Table 4.

There was no obvious evidence of Grade III/IV hematological or renal toxicity in any of the patients during the follow-up period.

At the time of assessment, two patients had expired and six patients were alive. On symptomatic response scale, complete disappearance of symptoms was found in one patient (12.5%), three patients (37.5%) showed partial improvement in symptom after PRRT, whereas four patients (50%) showed worsening of and appearance of new symptoms. On biochemical response, reduction in serum TG was found in three patients (37.5%) after PRRT and increase in serum TG was noticed in the rest of the five patients (62.5%). Imaging response showed stable scan finding in two patients (25%) and PD in six patients (75%), following a progression-free survival ranging from 7 to 16 months, when they were considered for TKIs in view of PD.

Table 1: Patients characteristics

Characteristics	Values
Age distribution (years)	57-83
Sex (male: female)	5:3
Sites of metastases	Thyroid Bilateral lung (nodules) Pretracheal and paratracheal nodes Anterior mediastinum Right fibula Right ischium Multiple vertebrae
Grade of ⁶⁸ Ga-DOTATATE/ ^{99m} Tc-HYNIC-TOC uptake (semiquantitative scale)	
Grade 0 (no uptake)	0
Grade I (less than liver)	1
Grade II (equal to liver)	6
Grade III (more than liver)	1

Table 2: Patient and lesion specific histopathological characteristics

Patient	Site of metastases	Histopathological characteristics
Case I	Thyroid, bilateral lung nodules	Metastatic FVPCT
Case II	Right supraclavicular, right paratracheal, bilateral lung	Differentiated PCT
Case III	Anterior mediastinum Right lung Left level III cervical node	Differentiated PCT
Case IV	Bilateral lung	Differentiated PCT
Case V	Retropharyngeal mass	Follicular carcinoma thyroid
Case VI	Right fibula Skull Left 6 th rib Bilateral pelvic bone	Poorly differentiated Ca thyroid
Case VII	Multiple vertebrae Bilateral lung	Differentiated PCT
Case VIII	Bilateral lung, bony lesions	FVPTC

Ca: Carcinoma; PCT: Papillary carcinoma thyroid; FVPCT: Follicular variant of papillary carcinoma thyroid

Table 3: Evaluation of somatostatin receptor based imaging and fluorodeoxyglucose-positron emission tomography at baseline

Patient	⁶⁸ Ga-DOTATATE/ ^{99m} Tc-HYNIC-TOC	FDG-PET/CT (SUV _{max})
Case I	Grade I	13
Case II	Grade II	15
Case III	Grade II	8.6
Case IV	Grade II	7.5
Case V	Grade II	23.46
Case VI	Grade III	6.2
Case VII	Grade II	13
Case VIII	Grade II	13

FDG-PET/CT: Fluorodeoxyglucose-positron emission tomography/computed tomography; SUV_{max}: Maximum standardized uptake value

DISCUSSION

SSTR-based theranostics has been a recent development in the management of NETs, which incorporates molecular imaging with either gamma camera and single-photon emission CT-based tracers (e.g., ^{99m}Tc-HYNIC-TOC/¹¹¹In-DTPA-octreotide)

or more preferably with PET-based tracers such as ⁶⁸Ga-DOTA-NOC/TATE, which offer the advantages of better resolution and quantification useful for treatment response evaluation. The therapy is undertaken with either ¹⁷⁷Lu or with ⁹⁰Y labeled somatostatin analogs (such as ¹⁷⁷Lu-DOTA-TOC/TATE or ⁹⁰Y-DOTA-TOC), which has been immensely successful in metastatic GEP-NETs. The TENIS has been postulated as a potential indication of PRRT in patients who demonstrate substantial tracer avidity on ⁶⁸Ga-DOTATATE-positive scan. There is at present relative paucity of literature data on the efficacy of PRRT in patients with TENIS.^[15-17]

Budiawan *et al.*^[15] studied 16 nonradioiodine-avid and/or radioiodine therapy-refractory thyroid cancer patients that included follicular thyroid carcinoma (*n* = 4), medullary thyroid carcinoma (*n* = 8), Hürthle cell thyroid carcinoma (*n* = 3), and mixed carcinoma (*n* = 1). These patients were treated with PRRT using (90) Yttrium and/or (177) Lutetium labeled somatostatin analogs. No specific subdivisions were made in this study. There was disease stabilization in four (36.4%) patients, partial remission (PR) in two patients (18.2%), PD in five patients (45.5%).

Versari *et al.*^[16] reported 11 patients treated with PRRT with fractionated injection of 1.5–3.7 GBq ⁹⁰Y-DOTATOC, of which disease control was achieved in seven patients (two PR and five stabilization), with a duration of response of

3.5–11.5 months. The authors concluded that functional volume over time obtained by PET/CT was the only parameter demonstrating a significant difference between lesions responding and nonresponding to PRRT.

Czeczynski *et al.*^[17] studied 11 patients of radioiodine-refractory differentiated thyroid cancer treated with PRRT. Fractionated treatment protocol with four doses of ⁹⁰Y-DOTA-TOC in 12-week intervals was employed in these patients, and the activity of each dose administered was 3.7 GBq (100 mCi). Of the 11 patients, 5 died before receiving the fourth course of PRRT. In the remaining six patients, morphological response, evaluated 3 months after the last course using the RECIST criteria, showed PR in one patient, SD in two patients, and PD in three patients. Biochemical response based on TG measurements before and after PRRT showed PR in one patient, SD in four patients, and PD in one patient. The median survival was 21 months from the first course of PRRT.

A comparison was drawn with the findings of previous studies and our findings in the present analysis. In our series, among the eight patients of TENIS, partial biochemical response was noted in three patients (37.5%). On imaging response evaluation, SD was observed in two patients (25%), whereas most demonstrated a PD after 7–16 months of PFS. In addition, we also observed that most patients of TENIS showed low-grade uptake on SSTR-based imaging (Grade 2 as per our semi-quantitative scale), with only one patient showing Grade 3 uptake [Figure 1]. This is similar to what was observed in our previous series.^[19]

Unlike GEP-NET, there is relatively less percentage and obvious objective response to PRRT in thyroid cancer patients, the reason for which this therapy has not been employed widely in this group of patients. Many patients with these malignancies are usually asymptomatic, especially patients with TENIS. Thus, at times, it is difficult to classify them on symptomatic scale, and maintenance of asymptomatic status would usually qualify as SD during response assessment.

Table 4: Individual patient specific treatment details

Patient	Number of cycles of PRRT given (cumulative activity in GBq)	Duration of follow-up from 1 st cycle of PRRT (months)
Case I	3 cycles (17.24)	24
Case II	1 cycle (6.7)	36
Case III	1 cycle (5.5)	12
Case IV	4 cycles (25.4)	43
Case V	2 cycles (10.0)	52
Case VI	2 cycles (10.8)	48
Case VII	1 cycle (6.7)	7
Case VIII	4 cycles (25.4)	50

PRRT: Peptide receptor radionuclide therapy

Table 5: Patient specific hematological and renal toxicity

Patient	Hematological toxicity			Renal toxicity		
	Anemia	WBC	Platelet count	Serum creatinine	GFR	ERPF
Case I	-	-	-	-	-	-
Case II	-	-	-	-	-	-
Case III	-	-	-	-	-	-
Case IV	-	-	-	+ (Grade I)	++ (Grade II)	++ (Grade II)
Case V	-	-	-	-	-	-
Case VI	-	-	-	-	-	-
Case VII	-	-	-	-	-	-
Case VIII	-	-	-	-	-	-

WBC: White blood cell; GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; -: No toxicity observed; +: Toxicity with grade in brackets

Table 6: Response assessment

Response	Symptomatic (%)	Biochemical (%)	Scan (%)
CR	1 (12.5)	0	0
PR	3 (37.5)	3 (37.5)	0
SD	0	0	2 (25)
PD	4 (50)	5 (62.5)	6 (75)

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease

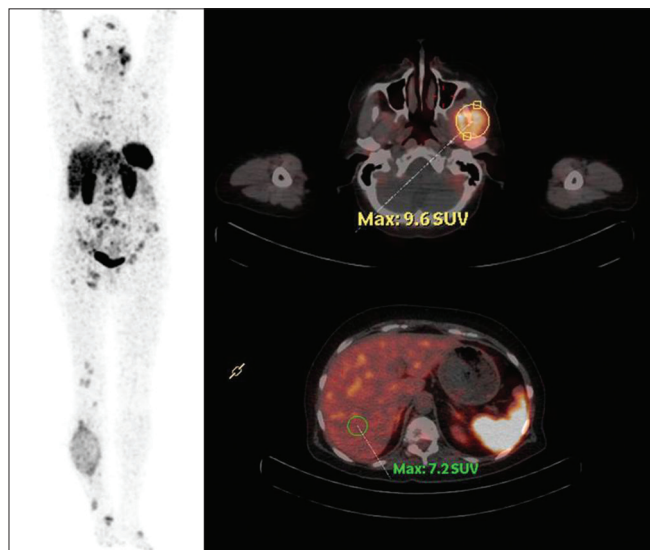


Figure 1: ⁶⁸Ga-DOTATATE positron emission tomography/computed tomography in a patient of thyroglobulin-elevated negative iodine scintigraphy demonstrating Grade III uptake in a number of the skeletal metastatic lesions

From the previously reported studies and the result of this study, it appears that PRRT with ¹⁷⁷Lu-DOTATATE is modestly useful in metastatic TENIS and does not produce remarkable improvement akin to that observed in metastatic GEP-NET. A few explanations could be made for the relative inefficacy of PRRT in thyroid tumors as follows: (i) the relatively low-grade SSTR expression and low-grade ⁶⁸Ga/¹⁷⁷Lu-DOTATATE avidity in general in this group of patients is usual and correspondingly the targeting by the therapeutic agent is relatively low compared to GEPNETs and (ii) most of the TENIS patients usually have FDG-avid disease, the high FDG avidity is commensurate with aggressive biology and could be the reason for their relatively low response.

CONCLUSION

In metastatic TENIS patients, PRRT may be considered a therapeutic option with minimal toxicity, depending on SSTR expression in these cases with a fraction of patients showing promising response [Tables 5 and 6]. A larger patient population need to be examined using other radiopeptides with higher affinity to the predominantly expressed SSTR subtypes in thyroid cancer to confirm the benefit of PRRT in TENIS cases.

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Conflicts of interest

There are no conflicts of interest.

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