Original article

^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy in Metastatic or Advanced and Inoperable Primary Neuroendocrine Tumors of Rare Sites

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Abstract

The present study aimed at exploring the patient and imaging characteristics of primary neuroendocrine tumors (NETs) of rare sites who presented with metastatic and/or advanced inoperable stages and therefore was considered for peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE. A retrospective analysis was undertaken of these patients focusing on the aforementioned aspects. All patients underwent dual-tracer molecular functional imaging with somatostatin receptor (SSTR)-based imaging (with either ^{99m}Tc-HYNIC-TOC or ^{68}Ga-DOTATATE) and ^{18}fluorine fludeoxyglucose positron emission tomography-computed tomography as the pretherapy assessment. Based on the qualitative uptake of tracer in SSTR imaging, the lesions were divided into four categories Grade 0–III. The response was assessed post-PRRT by three parameters: (i) symptomatic response, (ii) biochemical response (serum tumor marker), and (iii) objective imaging response. The response profiles under each of these scales were assessed utilizing predefined criteria (detailed in methods). The overall response classification into partial response, stable disease, and progressive disease was done based on documentation of similar scale/category of at least two parameters among the triple parametric assessment. A total of nine patients (7 males, 2 females; age range: 33–59 years) with rare site primary NET were found: The primary sites included ureter (n = 1), sacrococcygeal (n = 1), esophagus (n = 1), thymus (n = 3), and mediastinum (n = 3). Treatment response assessment was undertaken in eight patients who received more than 2 cycles of PRRT with ^{177}Lu-DOTATATE. In this response assessment group (n = 8), the patients received 2–5 cycles and follow-up duration ranged from 5 to 48 months. Symptomatic responses and better quality of life were observed in 4/8 (50%) patients, stable symptomatic disease in 3/8 (37.5%), and progression in 1/8 patients (12.5%). Biochemically, partial response was seen in 3/8 (37.5%), stable values was seen in 3/8 (37.5%), and progression of tumor marker was seen in 2/8 (25%) patients. Morphologically, partial response was seen in 2/8 (25%), stable disease in 5/8 (62.5%), and progressive disease in 1/8 (12.5%) patients. On overall assessment, 2/8 patients (25%) demonstrated partial response, 4/8 stable disease (50%), and 2/8 progressive disease (25%) at the time of assessment. As per the RECIST 1.1, seven patients had stable disease and one patient had progressive disease. No specific correlation could be obtained between dual-tracer molecular imaging features and the response likely due to small population of the study group. Overall, there was evidence of excellent disease stabilization, and symptom palliation with ^{177}Lu-DOTATATE PRRT was documented in these advanced or metastatic NETs of various rare sites.

Keywords: ^{177}Lu-DOTATATE, neuroendocrine tumor, peptide receptor radionuclide therapy

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies and include different terminologies

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such as carcinoid tumors, noncarcinoid tumors, gastroenteropancreatic (GEP) tumors, vasoactive intestinal peptide-producing tumors, ganglioneuromas, small-cell lung cancers, and Merkel cell tumors.[1] These tumors either may present with functional or nonfunctional or may be familial associated with other tumors or neoplasms of endocrine system or sporadic.[1,2] The diagnoses of NETs are usually difficult and late due to nonspecificity of symptoms (such as abdominal pain and diarrhea), slow growth of tumor, and various anatomical locations of primary. The therapeutic options depend on site, size, and stage of the disease, with surgery being the treatment of choice, when it is feasible. Depending on the histopathological subtypes, sites of disease involvement, molecular imaging parameters, there have been attempts toward the development of personalized model and decision-making.[3-6] Tumors with high fludeoxyglucose (FDG) uptake tend to be more clinically aggressive. NETs when show strong affinity for FDG, the corresponding level of uptake in somatostatin receptor (SSTR)-based imaging tends to be low or absent, and conversely, when uptake is high with a radiolabeled SSTR imaging, FDG activity in the tumor tends to be low or absent.[7-10] Most of our clinical experience of peptide receptor radionuclide therapy (PRRT) has mostly been employed in NETs of the pancreas and gastrointestinal tract (GEP-NET) and lung. In this study, we analyzed the characteristics, imaging parameters, and response profile of patients with NET of uncommon sites, who have undergone PRRT at our center.

Materials and Methods

This was a retrospective audit of patients with histologically proven primary NET of rare sites and was treated with ^{177}Lu-DOTATATE. Inclusion criteria for the study were patients with histopathologically confirmed NET and inoperable or metastatic tumors referred for PRRT with ^{177}Lu-DOTATATE and were positive on SSTR imaging.

Based on the qualitative uptake of tracer in SSTR imaging (with either ^{99m}Tc-HYNIC-TOC or ^{68}Ga-DOTATATE), the lesions were divided into four categories: Grade 0: No uptake, Grade I: Uptake less than liver but more than background, Grade II: Uptake equal to liver, Grade III: Uptake more than liver [Table 1a].

The patients also underwent positron emission tomography-computed tomography (PET-CT) imaging with ^{18}fluorine-FDG (^{18}F-FDG) for characterization of lesions in comparison with SSTR imaging as to whether the lesions are concordant (positive in both imaging) and discordant (positive on SSTR imaging and negative on ^{18}F-FDG PET-CT) and whether these divisions had any impact in response outcome.

The PRRT with ^{177}Lu-DOTATATE was delivered following standardized protocol (150–200 mCi per cycle) at 3 monthly intervals up to 5 cycles.

Response evaluation

Response was assessed post-PRRT (minimum post 2 and maximum post 5 cycles of PRRT) under three headings – clinical/symptomatic response (subjective response), radiological/objective imaging response (^{18}F-FDG PET and SSTR imaging), and biochemical response (tumor marker). The time elapsed at the time of analysis ranged from 5 to 48 months following first PRRT cycle.

Scales or parameters of assessment and definition of categories in each individual parameter

For symptomatic response, complete response was defined as those where there was complete resolution of symptoms, partial symptomatic response when there was more than 25% resolution of symptoms compared to the baseline, stable symptomatic disease was defined as similar or <25% resolution of the symptoms and no new symptoms (for asymptomatic patient, this was defined as maintenance of asymptomatic status), and progressive symptomatic disease was defined as any appearance of new symptoms.

For biochemical response, partial biochemical response was defined as reduction of serum tumor marker more than 25% compared to baseline, stable disease as similar or any change of marker level within 25% of the baseline, and progressive disease as more than 25% increase in serum tumor marker level compared to the baseline.

For scan/imaging response, partial scan response was defined as more than 25% decrease in tracer uptake and/or reduction in number of lesions, stable disease as similar or any change within 25% of the baseline study, and progressive disease as more than 25% increase in either tracer uptake and/or increase in number of lesions. The uptake/activity was estimated using maximum standardized uptake value (SUVmax) and change in SUVmax expressed as percentage wherever available.

Overall response categories

Based on the aforementioned response category documentation in three individual parameters, the overall response was classified into partial response, stable disease, and progressive disease based on whether

there was documentation of similar scale/category in at least two parameters among the three (i.e., symptomatic, biochemical, and imaging response).

Observations and Results

The study population included nine patients (7 males, 2 females) with age ranging from 33 to 59 years [Table 1a], referred to our institute for PRRT. On the basis of site of primary lesions: 3 had thymic NET, 3 had mediastinal NET, and 1 each had ureteric, esophageal, and sacral NET, respectively [Table 1a and b]. Treatment response assessment was undertaken in eight patients who received more than 2 cycles of PRRT with ^{177}Lu-DOTATATE [Figures 1-4]. The imaging characteristics and the response in each individual patient are tabulated in Table 2. At the time of analysis, the patients received 1–5 cycles (5 cycles: 1 patient, 4 cycles: 3 patients, 3 and 2 cycles: 2 patients in each category, and 1 cycle: 1 patient) and follow-up duration ranged from 9 to 48 months (except for one patient with single cycle, who had received the same around 1 month before and was not included in the response assessment).

Symptomatic responses and better quality of life (complete response in two patients and partial response in two patients) were observed in 4 out of 8 (50%) patients, and stable symptomatic disease was observed in 3 out of 8 (37.5%) patients. Symptomatic progression was noted in 1 of 8 patients (12.5%) [Table 3].

Biochemically, partial response was seen in 3 of 8 (37.5%) patients, stable values was in 3 of 8 (37.5%), and progression of tumor marker was seen in 2 of 8 patients (25%) [Table 3].

Morphologically, partial response was seen in 2 of 8 (25%), stable disease in 5 of 8 (62.5%), and progressive disease in 1 of 8 (12.5%) [Table 3].

On overall assessment by the predefined criteria as assessed by each individual parameter, 2 of

Table 1a: Patient and lesion characteristics

Characteristics	Values
Age distribution (years)	33-59
Sex	
Male:female	7:2
Site of primary	
Thymus	3
Mediastinum	3
Ureter	1
Esophagus	1
Sacral NET	1
Grade of HYNIC/gallium uptake	
Grade 0 (no uptake)	0
Grade I (less than liver)	0
Grade II (equal to liver)	5
Grade III (more than liver)	5

NET: Neuroendocrine tumor

Table 1b: Patient and lesion specific histopathological characteristics

Patient	Site	Histopathological characteristics
Case I	Ureter	Neuroendocrine carcinoma Mib1: 15%
Case II	Esophagus	Intermediate grade NET Mib1: 7%
Case III	Mediastinum	Atypical carcinoid
Case IV	Thymus	Thymic carcinoid
Case V	Sacrum	NET
Case VI	Thymus	Atypical carcinoid
Case VII	Thymus	Typical carcinoid
Case VIII	Mediastinum	NET
Case IX	Mediastinum	NET (Mib1: 8-10%)

NET: Neuroendocrine tumor

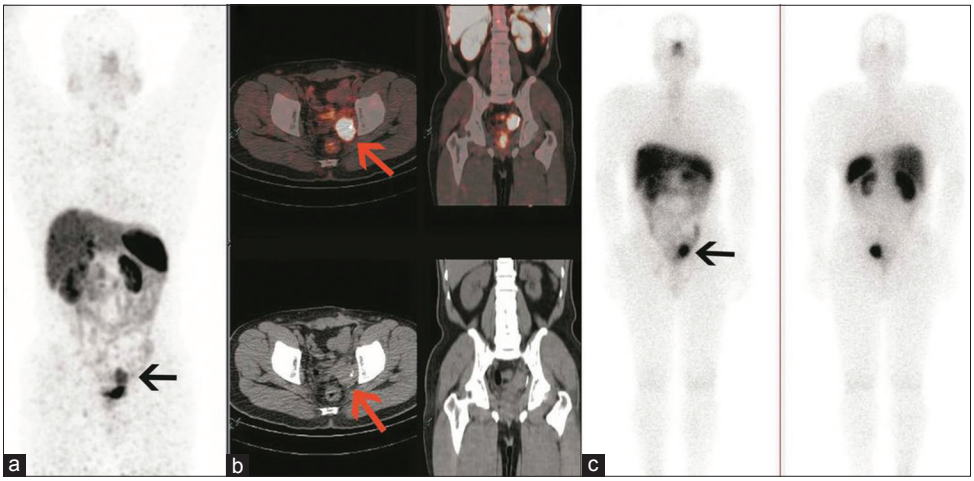

Figure 1: A known case of left ureteric neuroendocrine tumor. (a and b) ^{68}Ga-DOTATATE positron emission tomography-computed tomography (a and b) showing tracer avid soft tissue lesion pelvic region involving the left ureter. Posttherapy whole-body scan following ^{177}Lu-DOTATATE therapy (c) demonstrates adequate tracer uptake in left ureteric lesion. At 24 months, the patient had stable disease scanwise and biochemically and was asymptomatic

Table 2: Dual-tracer imaging characteristics along with response categorization in 3 individual scales

Case number	68Ga-DOTATATE/^{99m}Tc-HYNIC-TOC	FDG PET/CT	Treatment response in each of three parameters
Case I	Tracer avid left ureteric lesion	Non-FDG avid left ureteric lesion	Symptomatic: Complete response (100% improvement on symptom scale) Biochemical: Stable disease Scan: Stable disease
Case II	Tracer avid supraclavicular nodal, left adrenal lesion	FDG avid supraclavicular nodal, left adrenal lesion	Symptomatic: Complete response (100% improvement in symptoms) Biochemical: Stable disease Scan: Partial response
Case III	Tracer avid mediastinal lesion	FDG avid mediastinal lesion	Symptomatic: Progressive disease (symptom persists) Biochemical: Progressive disease Scan: Stable disease (visual analysis)
Case IV	Tracer avid pleural lesions, mediastinal lesion	FDG avid pleural lesions, mediastinal lesion	Symptomatic: Stable disease (20% improvement) Biochemical: Stable disease Scan: Stable disease
Case V	Tracer avid sacral lesion	FDG avid sacral lesion	Symptomatic: Partial response (30% improvement after 2 cycles) Biochemical: Stable disease Scan: Stable disease
Case VI	Tracer avid thymic lesion and pancreatic lesion	Non-FDG avid thymic lesion and pancreatic lesion	Symptomatic: Stable disease (asymptomatic) Biochemical: Partial response (25% decrease in CgA level) Scan: Partial response
Case VII	Tracer avid orbital, thymic, and mediastinal lesion	Non-FDG avid right orbital, thymic, and mediastinal lesions	Symptomatic: Partial response (80% improvement during initial 2 cycles followed by progressive disease thereafter) Biochemical: Partial response: After 2 cycles: 80% decrease in value Scan: Progressive disease (new lesion)
Case VIII	Tracer avid mediastinal lesion and pleural lesion	FDG avid mediastinal lesion and pleural lesion	First cycle 1 month before: Treatment response not undertaken
Case IX	Tracer avid mediastinal and skeletal lesion	None to faintly FDG avid mediastinal and skeletal lesion	Symptomatic: Stable disease: 20% improvement Biochemical: Partial response (~50% decrease in CgA level Scan: Stable disease

FDG: Fludeoxyglucose; PET: Positron emission tomography; CT: Computed tomography; CgA: Chromogranin A

Table 3: Response categorization as per the three different scales assessed individually

Response	Symptomatic	Biochemical	Functional scan	RECIST 1.1 (anatomical imaging)
CR	2	0	0	0
PR	2	3	2	0
SD	3	3	5	7
PD	1	2	1	1

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

8 patients (25%) showed partial response, 4 of 8 (50%) demonstrated stable disease, and 2 of 8 (25%) showed progressive disease [Table 4].

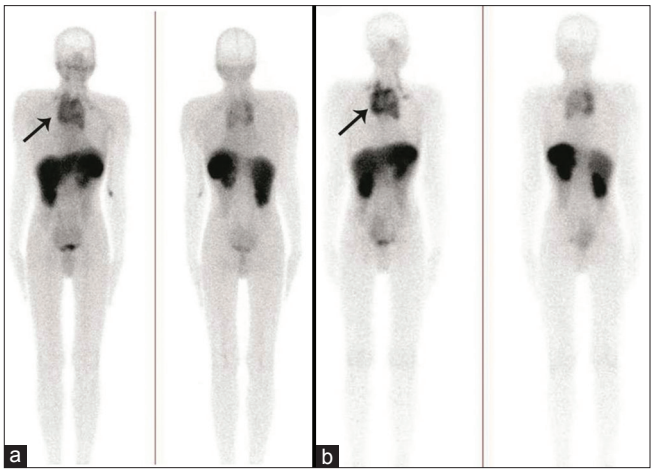

Figure 2: A 37-year-male patient a known case of atypical mediastinal carcinoid. ^{99m}Tc-HYNIC-TOC scan (a) showing tracer uptake in large mediastinal lesion and post-^{177}Lu-DOTATATE therapy scan (b) demonstrates analogous uptake of the therapeutic agent in the mediastinal lesion. The patient demonstrated progressive disease at 9 months while being worked up for the 3rd cycle peptide receptor radionuclide therapy and was considered for chemotherapy

Discussion

NETs generally overexpress SSTR, which have been targeted and successfully exploited for their treatment with PRRT. The guidelines for PRRT recommend unresectability of the lesion, metastatic disease, and demonstrating adequate tracer avidity on SSTR-based imaging such as ^{68}Ga-DOTATOC/NOC/TATE PET or ^{99m}TC-HYNIC-TOC/111In-DTPA-octreotide scintigraphy. In the present study, we have analyzed the patients with NETs of uncommon sites which were inoperable or metastatic and focused on the imaging

characteristics on dual-tracer imaging and efficacy of treatment with PRRT. All patients (except Case VIII who received1 cycle of therapy ^{177}Lu-DOTATATE) received at least 2 cycles of therapy with ^{177}Lu-DOTATATE.

Table 4: Overall response categorization

Category	Number of patients	Percentage
Responder	2/8	25
Stable disease	4/8	50
Progressive disease	2/8	25

In our study, we observed symptomatic response in a substantial fraction of symptomatic patients (with only one patient demonstrating symptomatic progression). The patient with progressive symptomatic disease, however, showed morphologically that the disease was stable with reduction in tumor marker profile. On overall assessment (combining three parameters), 50% of patients showed stable disease and 25% demonstrated partial response; taken together, disease control was observed in 75% of patients.

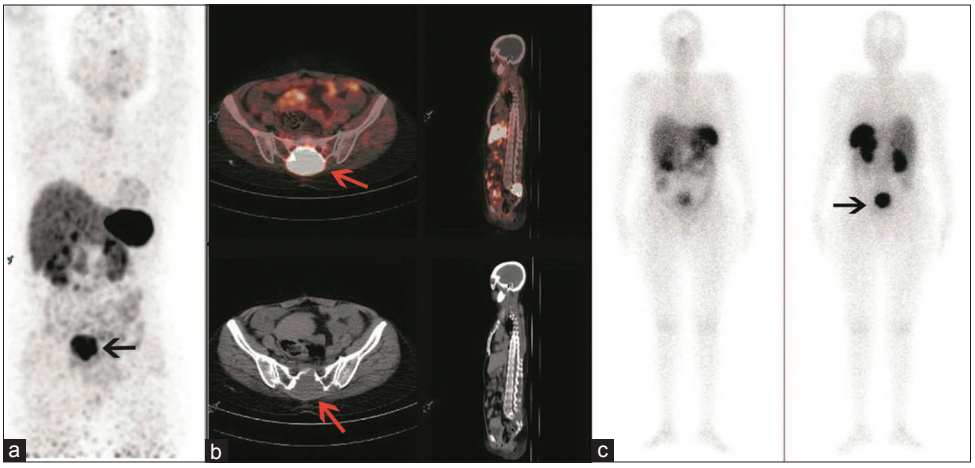

Figure 3: A female patient a known case of neuroendocrine tumors of sacrococcygeal region. ^{68}Ga-DOTATATE positron emission tomography-computed tomography (a and b) demonstrating tracer uptake in sacral primary lesion with lytic with soft-tissue component. The post-peptide receptor radionuclide therapy scan (c) showing adequate tracer uptake in the inoperable primary. At the time of the 3rd cycle workup, the patient had 30% improvement symptomatically, scanwise and biochemically stable disease. Following the 3rd cycle, she was considered for addition of local external radiotherapy in view of persistence of symptoms

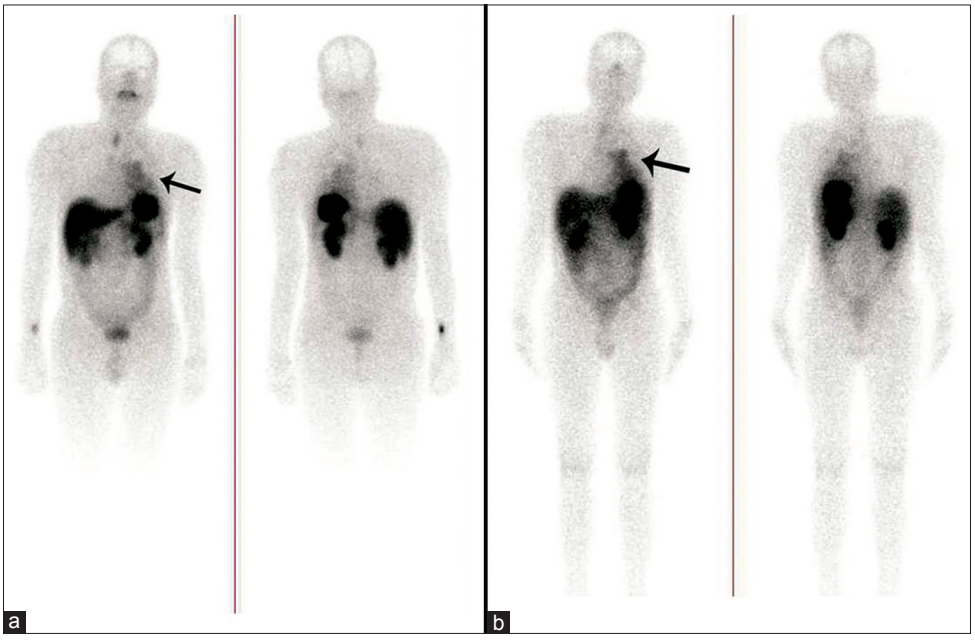

Figure 4: A 50-year-male patient a known case of thymic carcinoid and left pleural involvement with pleural-based nodule. ^{99m}Tc-HYNIC-TOC scan (a) tracer uptake in thymic lesion and left pleural-based nodule. Posttherapy scan (b) analogous tracer uptake in thymic lesion and left pleural-based nodule. The patient received 4 cycles of peptide receptor radionuclide therapy (213, 214, 134, and 140 mCi) last on August 5, 2015. At the time of assessment, the patient had stable disease in all 3 scales

All the above indicate excellent disease palliation with ^{177}Lu-DOTATATE in advanced NET of various rare sites. On dual-tracer approach for evaluation of any significant difference in outcome to therapy, no significant difference was appreciated due to small population of the study group, which needs to be further studied with further larger population sample for any possible implication to outcome to response to PRRT.

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Conflicts of interest
There are no conflicts of interest.

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