Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies and include different terminologies.
such as carcinoid tumors, noncarcinoid tumors, gastroenteropancreatic (GEP) tumors, vasoactive intestinal peptide-producing tumors, ganglioneuromas, small-cell lung cancers, and Merkel cell tumors.\cite{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.\cite{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.\cite{3-6,7-10}

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.\cite{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                            | Thy mus 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 carcinoma                     |
| 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 | 
|------------|------------|
| Case I     |            |
| Case II    |            |
| Case III   |            |
| Case IV    |            |
| Case V     |            |
| Case VI    |            |
| Case VII   |            |
| Case VIII  |            |
| Case IX    |            |
| Case X     |            |

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

**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 68Ga-DOTATOC/NOC/TATE PET or 99mTc-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 received 1 cycle of therapy $^{177}$Lu-DOTATATE) received at least 2 cycles of therapy with $^{177}$Lu-DOTATATE.

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.

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

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 177Lu-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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