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Editorial

Peptide Receptor Radionuclide Therapy in the Management of Neuroendocrine Tumors (Neoplasms)*: Fundamentals and Salient Clinical Practice Points for Medical Oncologists

Abstract

This editorial commentary is an expert summary of "Peptide Receptor Radionuclide Therapy (PRRT)," encompassing the essential fundamentals and salient clinical practice points, deliberated and designed in a point-wise manner with theme-based subheadings. Emphasis has been laid on the topics of practical relevance to the referring oncologists with relevant finer points where necessary. A part of the presented overview has been generated from the authors' own practical experience of more than 3500 successful therapies delivered over the last 9 years at a large tertiary care PRRT setting by the joint efforts of Radiation Medicine Centre (RMC), Bhabha Atomic Research Centre (BARC), and Gastrointestinal services of Tata Memorial Hospital (TMH) at the TMH-RMC premises. While the technical indigenization is beyond the scope of this treatise, we must mention here that India had been one of the frontrunners in this treatment modality, and the PRRT services in this country were developed purely as an indigenous effort right from the production of the radionuclide (177-Lutetium) at the reactor and radiolabeling and production of the radiopharmaceutical (^{177}Lu-DOTATATE) by the radiopharmaceutical scientists at the BARC and RMC; such an endeavor allowed this very specialized therapy to be delivered at a very affordable cost in our setting which could be viewed as a major societal contribution of the atomic energy research in this country.

Keywords: *Neuroendocrine tumor, neuroendocrine neoplasm, peptide receptor radionuclide therapy (PRRT), Somatostatin receptor imaging, ^{68}Ga-DOTATATE PET-CT, ^{99m}Tc-HYNIC-TOC SPECT, FDG-PET/CT, ^{177}Lu-DOTATATE, ^{90}Y-DOTATOC*

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Principle of Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) is a molecular targeted receptor-based radiopeptide therapy for metastatic/advanced neuroendocrine neoplasms (NENs), delivered through an intravenously administered unsealed radioisotope source (mostly lutetium octreotate or ^{177}Lu-DOTATATE).[1] The fundamental principle is targeting somatostatin receptors (SSTRs), a family of G-protein-coupled receptors comprising five distinct subtypes (*SSTR1* to *SSTR5*), of which subtype 2 ($SSTR_2$) has been of the major target in PRRT, in view of its overexpression and dominance in the NENs.

The therapy is based on the principle of "Theranostics" ("Treat what you see and See what you treat"), which is defined by integrating a diagnostic testing (in this case, diagnostic agent and modality: ^{68}Ga-DOTA-TOC/NOC/TATE for positron emission tomography [PET] imaging and ^{99m}Tc-HYNIC-TOC as single-photon emission computed tomography [SPECT] imaging where the former is not available) for the presence of a molecular target (in this case, SSTR2), for which a specific treatment/drug is intended (mostly lutetium octreotate or ^{177}Lu-DOTATATE).

On the Radiopharmaceutical: why OCTREOTATE (DOTATATE) Preferred Vis-a- Vis Octreotide?

While Tyr3-octreotide (TOC) had been initially used in several centers (in the

* As per the International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus recommendations in 2017, the authors would use the term "Neoplasms" rather than "Tumors" throughout the document.[1]

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form of 90Y-DOTATOC/^{177}Lu-DOTATOC), it has by far now replaced by ^{177}Lu-DOTATATE worldwide. Octreotate differs from octreotide in that the C-terminal threoninol (a corresponding amino alcohol) is replaced by threonine. This chemical modification had resulted in nearly ninefold increase in the affinity of (DOTA 0, Tyr 3) octreotate for the SSTR 2 when compared with (DOTA 0, Tyr 3) octreotide. This translates into 6- to 7-fold increase in affinity for their radiolabeled counterparts and finally 4–5 times enhancement in the tumor uptake and dose delivery.

Patient Selection for Peptide Receptor Radionuclide Therapy: The Typical and Extended Indications

Metastatic and unresectable neuroendocrine tumors that demonstrate high-grade uptake (semi-quantitative Krenning score 3 or 4) on SSTR-based ^{68}Ga-DOTA-TOC/TATE PET-computed tomography (PET-CT) and ^{99m}Tc-HYNIC-TOC SPECT-CT are the ones being considered for PRRT. Such patients typically encompass well-differentiated and moderately differentiated NENs (NEN Grade 1 or 2 according to the World Health Organization 2017 classification, with Ki-67/MIB-1 labeling index (LI) up to 20%, though some guidelines European Society for Medical Oncology (ESMO) recommend considering patients up to Ki67 of 30%.[2,3] The Krenning score is a semi-quantitative scoring system used to grade the uptake intensity of metastatic NEN lesions on SSTR-based imaging.[4] The usual setting has been disease progression on cold somatostatin analogs (SSAs), though the application of PRRT has been steadily growing and sometimes being considered upfront in patients with large-bulk disease on diagnostic study.

Finer points on extended indications

While the aforementioned has been a typical indication for PRRT in NENs, there have been a number of "stretching the boundaries" beyond the typical indication in view of the excellent tolerability of PRRT and gratifying results in improving the quality of life in this group of patients, as follows:

a. PRRT in NENs with MIB-1 (Ki-67) LI between 20% and 30%: This is a "gray zone" and frequently, these group of tumors demonstrate high uptake on ^{68}Ga-DOTATATE PET-CT and has been an area where PRRT has been advocated successfully.[5] In addition, this group usually demonstrates high uptake of fluorodeoxyglucose (FDG) (on dual-tracer PET-CT), and thus combined chemo-PRRT is now an available option with encouraging results (detailed later). As previously mentioned, the ESMO clinical practice guidelines for gastroenteropancreatic (GEP)-NENs advocate PRRT up to Ki-67 of 30%[3,5]
b. Beyond GEP-NENs: While GEPNENs have been the major and classical indications of PRRT, there are a number of other areas where this therapy has been frequently considered and advocated. We do have a fair amount of clinical experience in these "beyond GEP-NEN" applications in our setting which include the following (in decreasing order of frequency):

i. Metastatic/inoperable Bronchopulmonary and Mediastinal/Thymic NENs,[6,7]
ii. ** Metastatic/inoperable Medullary thyroid carcinoma,
iii. Non-131I-MIBG concentrating metastatic Paraganglioma and Pheochromocytoma
iv. **Non-iodine concentrating metastasis of differentiated thyroid carcinoma (TENIS: only 15-20% of this patient subgroup demonstrates enough uptake to justify PRRT),[8]
v. Other tumors with neuroendocrine tumor differentiation/characterization: We have experience in metastatic Merkel Cell carcinoma, Menigioma and recurrent/inoperable Phosphaturic Mesenchymal Tumor.[9-11]

** In these '**' marked case scenarios, PRRT has been considered even though there was a lesser degree of uptake (Krenning score 2) on SSTR based scanning, esp due to alternative regimens were either potentially toxic/experimental with less-than-modest efficacy/expensive.

Decision-Making Workup Scans for ^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy

The first decision-making scan to judge the suitability of PRRT is SSTR-2 targeting ^{68}Ga-DOTATATE PET-CT (alternatively, other SSTR-based ligands, e.g., ^{68}Ga-DOTA-TOC/NOC PET-CT has also been used with equivalent diagnostic performance). The (i) superior resolution of PET-CT and (ii) the ability of quantification of uptake make ^{68}Ga-DOTATATE PET-CT the choice for evaluating NENs.[12,13]

However, in the Indian setting, ^{68}Ga-DOTATATE PET-CT may not be available to all centers (though the situation is rapidly changing), either due to (i) nonavailability of PET or (ii) nonavailability of ^{68}Ge-^{68}Ga generator which are mandatory components for the aforementioned scan. In centers where ^{68}Ga-DOTATATE PET-CT is not available, ^{99m}Tc-HYNIC-TOC SPECT is the preferred scan possible with conventional gamma camera. The kit formulation method and indigenous production at Bhabha Atomic Research Centre and Board of Radiation and Isotope Technology have made it readily available. The widespread employment of ^{99m}Tc-HYNIC-TOC possible at many peripheral centers without PET-CT is less known to many practitioners, who should ask this from their nuclear medicine colleagues. We must mention here that in our setup, in the initial years of PRRT development, ^{99m}Tc-HYNIC-TOC planar and SPECT imaging had served reasonably well (though quantification and the superior resolution of ^{68}Ga-DOTATATE PET-CT make it the preferred option); the message is where PET-CT is not available, ^{99m}Tc-HYNIC-TOC can be used for the decision-making [Figure 1].[14]

Dual-Tracer Positron Emission Tomography-Computed Tomography: important Value of Adding Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography to the Management Algorithm and Reading it Side-by-Side Somatostatin Receptor-Based Imaging for Personalized Decision-Making

The relative uptake of ^{68}Ga-DOTATATE and FDG in the tumor has evolved as a powerful indicator of assessing the dynamic tumor biology of NENs on a continuous scale.[15-18] This parameter has been well recognized in most active PRRT centers, and the medical oncologists at our setup are quite accustomed to interpretation of these studies. Along with the tumor Ki-67/MIB-1, ^{68}Ga-DOTATATE/FDG relative uptake forms an additional parameter to depict the tumor phenotype. The dual-tracer PET-CT results forms a scientific basis for personalizing therapy in NENs between SSA/PRRT vis-a-vis chemotherapy vis-a-vis chemo-PRRT. The latter is considered when there is high uptake on both scans and typically can be observed in Ki-67 between 20% and 30%, but can also be observed on occasional cases in tumors with Ki-67 LI between 10% and 20%.

We have started understanding that the dual-tracer PET-CT forms a valuable complementary to provide the subtle impression on tumor biology that cannot be discerned by the Ki-67 discrete value alone. In addition, in a real-world scenario, discordance can be occasionally observed between the dual-tracer PET-CT impression and that by the Ki-67 LI, when the former is frequently assigned more weightage by oncologists for taking decisions. Furthermore, due to intratumoral heterogeneity, the Ki-67 index of a biopsy specimen may not be representative of the entire tumor; thus in case of discordance between biopsy and imaging, the molecular imaging can result in better depiction of the tumor biology. In our experience, in day-to-day practice in a busy setting, even tumors <5% can demonstrate these characteristics. The emerging role of dual scans has shown heterogeneous behavior in many of the previously considered well-differentiated NENs.

Thus, areas where this can be of potential help in deciphering the tumor biology are: (i) tumors in the intermediate level of Ki-67 LI, for example, 10%–20%; (ii) tumors with Ki-67 LI between 20% and 30% (plays important and robust role for deciding between PRRT, chemo-PRRT, and chemotherapy); and (iii) cases showing discordance between Ki-67 and the dual-tracer PET-CT findings.[15,16]

Treatment Schedule and Brief Description

Typically, the PRRT cycles are administered at 8–12 weeks' interval, with an average of 150–200 mCi (5.55–7.4 GBq) in each cycle. In our setting, we usually keep (a) high-end dose (200 mCi) for a patient undergoing PRRT in a neoadjuvant setting with a short time interval (8 weeks between two cycles), whereas in the (b) multiple metastatic setting, a patient receives a mean of 150 mCi per cycle at 3-month intervals. On an average, a patient receives 4–5 cycles. While in the conventional fixed-dose regimen, a cumulative dose of 800 mCi is maintained (which is much within safe limits); it needs to be mentioned that with the dosimetric protocol, it is conveniently possible to administer further doses in most patients – this is to be factored into while considering "salvage PRRT" in case of progression/recurrence in the follow-up period or considering adding stereotactic body radiation therapy. The hematological and renal parameters can serve as good indirect guide for this.

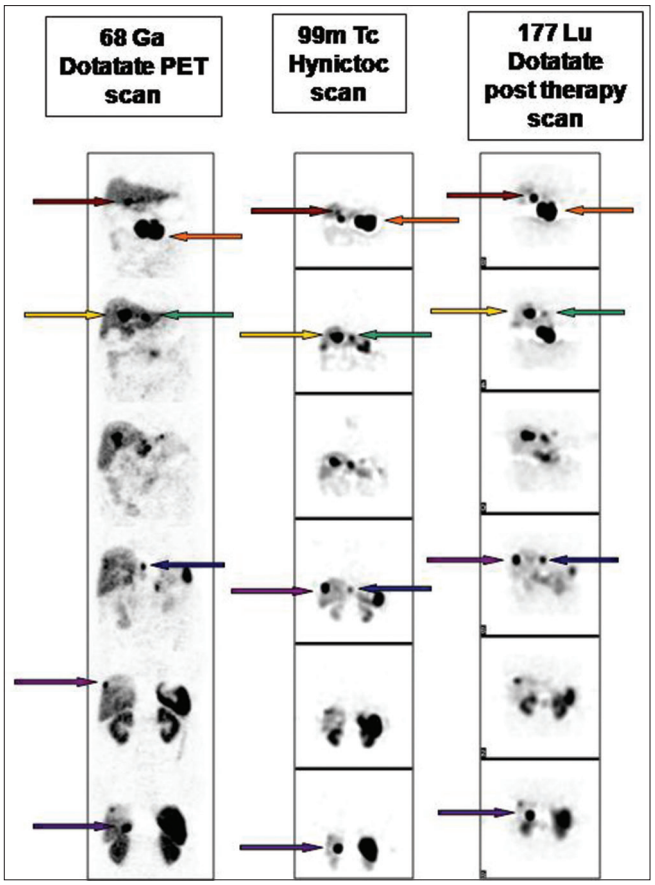

Figure 1: Comparison among ^{68}Ga-DOTA-TATE positron emission tomography/computed tomography, ^{99m}Tc-HYNIC-Tyr3-octreotide single-photon emission-computed tomography, and posttreatment ^{177}Lu-DOTA-octreotate single-photon emission-computed tomography for the detection of particular lesions. Arrows of the same color indicate the same lesion

The other point is that there is no randomized evidence for using neoadjuvant PRRT at present; good cytoreduction can be observed with PRRT in isolated patients as per our practice which can be used in the neoadjuvant setting on a case-to-case basis or in the research setting.

Renal protection is carried out with a mixed amino-acid infusion (1000 ml), infused over 8 h in addition to 200 ml prior to the ^{177}Lu-DOTATATE administration of the

treatment. While many nephroprotection protocols exist (ranging from 3 h infusion of basic amino acids to 2-day or 3-day protocol), in our experience, this envisaged protocol has given excellent results in addition to being convenient in a busy PRRT setting.

Contraindications and adverse effects and their management

First of all, PRRT is a well-tolerated therapy with minimal side effects, which is one of the reasons for its gaining popularity over the years among patients and the attending oncologists alike. One dose-limiting toxicity of PRRT has been nephrotoxicity at higher doses owing to the uptake of radiolabeled SSAs in the proximal tubule cells through megalin/cubulin system. The renal toxicity has been more often described in the context of ^{90}Y-DOTATATE due to its stronger beta energy, whereas with ^{177}Lu-DOTATATE, this adverse effect is substantially lower in incidence. The proposed cumulative absorbed dose to the kidney is limited to <23 Gy, which the standard PRRT protocols had hardly ever attained. Nonetheless, we keep watching over the following three particular group of patients: patients already having renal compromise due to (i) hypertension, (ii) diabetes mellitus, and/or (iii) prior chemotherapy. To achieve kidney protection, co-administration of basic amino acids through the other hand is undertaken as a routine in PRRT, which interferes with the reabsorption pathway. In our experience on a very large number of patients, we find excellent safety profile of ^{177}Lu-DOTATATE, including patients with a single functioning kidney.[19,20]

The other adverse effects are minimal: nausea and vomiting (primarily due to the amino acid co-infusion rather than the radiopharmaceutical *per se*) which, during or soon after the therapy, can be well managed with dexamethasone-ondansetron pretreatment or with aprepitant. Adequate blood counts (red blood cell, white blood cell, and platelets) are ensured prior to PRRT in order to prevent isolated incidences of long-term myelosuppression, specifically when combining with chemotherapy.

Efficacy results in metastatic settings

Probably, the most gratifying result is that in >90% of patients (esp. those with functioning NENs even uncontrolled with octreotide LAR), there is remarkable symptomatic improvement and better quality of life (QoL). The biochemical response in terms of reduction of serum CgA/urinary 5-HIAA is noted in 60%–70% of patients. On imaging, there were partial objective responses in around 30% of patients (complete response in 2%–6%) [Figure 2], whereas disease stabilization was achieved in nearly 60% who had otherwise demonstrated progressive disease on octreotide or lanreotide.[21-25]

In addition to the remarkable improvement in QoL even in patients with bulky disease, the other parameter of interest is the prolonged progression-free survival (PFS) achieved with PRRT. A Phase III multicentric international study (NETTER-1) in patients with inoperable, progressive, SSR-positive, midgut carcinoid tumors documents extremely promising results demonstrating a PFS of approximately 40 months versus 8.4 months for octreotide LAR. This appears to be substantially superior to other systemic treatment modalities available for metastatic NENs.[26]

There is some tumor-specific trend that can be observed: best objective responses can be seen in GEP-NENs, and similar response rates have been achieved in bronchopulmonary NENs, while relatively less favorable results are seen in thymic NENs and medullary thyroid carcinoma, when objective partial responses are concerned. However, for both of the latter, we have observed prolonged PFS, halting and stabilizing the disease.[6,7] Thus, there has been encouragement in recent times to advocate PRRT in these tumors if they demonstrate good uptake in the diagnostic study.

Strong points of peptide receptor radionuclide therapy vis-a-vis the newer targeted agents

The treatment options available for the advanced and metastatic NEN include systemic therapies such as SSAs, molecular targeting therapies, chemotherapy, and PRRT. The strong points of PRRT vis-a-vis the newer targeted agents (sunitinib and everolimus) include (a) targeted biological action/rationale of PRRT as well as limited side effect profile versus the toxicity of the new drugs, (b) the very convenient treatment schedule of PRRT (completed in few discrete 1-day cycles) versus requirement to be on these agents till disease progression, and (c) cost difference

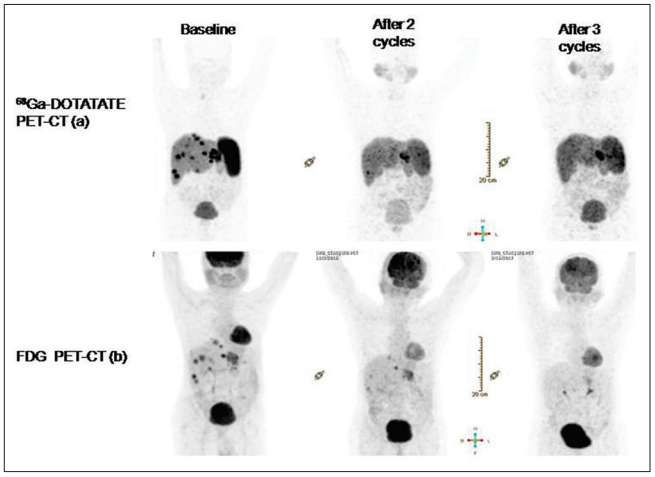

Figure 2: Excellent response obtained with ^{177}Lu-DOTATATE peptide receptor radionuclide therapy in a 70-year-old male, diagnosed as primary NET of body and tail of pancreas with multiple hepatic metastasis, MIB-1 index: 12% and no previous surgical intervention. Dual-tracer positron emission tomography-computed tomography ^{68}Ga-DOTATATE positron emission tomography (a) and fluorodeoxyglucose-positron emission tomography (b) demonstrating Krenning Grade IV uptake on baseline ^{68}Ga-DOTATATE positron emission tomography (upper-left image) with relatively low-grade fluorodeoxyglucose (lower-left image). Following three cycles of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy, the metastatic lesion in both scans showed excellent response, whereas the primary tumor showed partial response which was then considered for surgery. (Reproduced with permission from Basu *et al*.[14])

and expense (particularly related to our setting in view of indigenous production of the radiopharmaceutical).

Special case scenarios

"Sandwich" chemo-peptide receptor radionuclide therapy regimen in neuroendocrine neoplasms with high ^{68}Ga-DOTATATE and ^{18}F-fluorodeoxyglucose uptake on dual-tracer positron emission tomography/computed tomography

Inoperable and metastatic NENs with low Ki-67 index (usually positive for SSTR imaging with low/absent FDG uptake) are treated with SSA and PRRT, whereas NENs with high Ki67 index (that are usually negative on SSTR-based imaging and show high uptake on FDG-PET) are treated with chemotherapy. However, there exists an intermediate gray zone with the tumor demonstrating both high ^{68}Ga-DOTATATEand ^{18}F-FDG uptake on dual-tracer PET/CT, where a combined approach of PRRT plus chemotherapy appears a logical and rational approach.[27,28] In this regimen, two cycles of CAPTEM chemotherapy are sandwiched between two PRRT cycles of ^{177}Lu-DOTATATE. Thus, a typical schedule is PRRT followed by two cycles of CAPTEM followed by PRRT. In our setup, standard CAPTEM regimen comprising of oral capecitabine, 750 mg/m^2 twice daily for 14 days (D1–D14), and oral temozolomide 200 mg/m^2, once daily for 5 days (D10–D14) is followed by 2-week rest period and another CAPTEM cycle given for a total of 28 days is followed by the next cycle of PRRT at around 3 months. The response evaluation involves standard procedure, i.e., assessment in three scales namely (a) symptomatic scale, (b) biochemical tumor marker responses (serum CgA), and (c) imaging response with ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT. In our preliminary experience in a total of 38 aggressive metastatic NEN patients treated with chemo-PRRT, we found encouraging results with partial response in around 45%, stable disease in 39%, and progressive disease in 16% on RECIST 1.1 (unpublished data). The "chemoPRRT" regimen procedure was well tolerated in all the 38 patients, with no Grade III/IV hematological and renal toxicity in any of these patients.

Neoadjuvant peptide receptor radionuclide therapy

Similar to other oncological settings, neoadjuvant PRRT therapy has been examined for its ability to reduce the size of tumor in GEP-NENs to the point where an initially unresectable tumor becomes operable. PRRT as a neoadjuvant therapy was initiated in our setting to treat locally advanced GEP-NENs using the National Comprehensive Cancer Network criteria defined for borderline resectable pancreatic ductal adenocarcinoma. In our preliminary experience, the inoperable disease became operable in around 26% of patients in a population of 57 patients following PRRT. The PRRT was well tolerated in all the 57 patients, without any major hematologic or renal toxicity in any of these patients. We believe that this area needs further exploration, and surgeons must be encouraged to undertake studies which would be important to know the tumor characteristics that would be amenable to such intervention and to decide on its optimal protocol.

Resistant functioning neuroendocrine neoplasm with carcinoid syndrome

While PRRT is an excellent and effective therapeutic modality in functioning NENs in controlling the symptoms of carcinoid syndrome that are resistant to conventional therapies (e.g., octreotide/lanreotide), the effect, at times, may take 2–3 cycles, especially those with bulky hepatic metastases;[29] thus, it is needed to continue varying combinations of long-acting and short-acting octreotide to be administered in the interim months between the cycles (long-acting formulation intramuscularly) and just prior to therapy (short-acting formulation subcutaneously daily, which can be continued till 1 day prior to a ^{68}Ga-DOTATATE scan or PRRT). The patient preparation is quite important in these cases to prevent carcinoid crisis following PRRT (a rare but possible condition), which can be well obviated by good preparation.[30] In our setting, in a patient with symptomatic carcinoid syndrome, we advocate short-acting octreotide injections (subcutaneous) till 1 day before administering PRRT and start back the next day following PRRT and continue till 10–14 days after therapy. Furthermore, in a patient with bulky hepatic metastases, priming with antiserotonergic agent (e.g., cyproheptadine) is regularly undertaken.

Which radionuclide: ^{177}Lu, ^{90}Y, or alpha emitters?

PRRT has been traditionally performed with the following two beta emitters: yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu).[2] The radionuclides differ in their physical characteristics, which has a bearing on their efficacy and toxicity.[2] ^{90}Y possess a higher beta particle energy ($E\beta_{max}$ = 2.28 MeV) than ^{177}Lu ($E\beta_{max}$ = 0.497 MeV), and thus may be more suited to treating larger tumor masses but has more toxicity such as renal toxicity with ^{90}Y.[2] The recorded significant permanent renal toxicity from a Swiss study in over 1000 patients was documented quite high with ^{90}Y-DOTATOC at 9%.[31] This is one major reason why ^{177}Lu-DOTATATE has been and being adopted in most PRRT centers across the world, which has demonstrated an excellent safety profile in thousands of patients. We believe that combining 1–2 cycles of ^{90}Y-DOTATATE to the traditional ^{177}Lu-DOTATATE could be a reasonable approach for patients with large-sized heterogeneous tumors, although this needs to be examined in future trials. Recently, alpha emitter therapy (with ^{225}Ac-DOTATATE) has been introduced in the parlance of PRRT, which is theoretically promising in view of its (i) high linear energy transfer, implying delivery of "more powerful" radiation, and (ii) lesser penetration to the surrounding normal

tissues (thus lesser toxicity), though the clinical results are awaited to prove this impression.

Cost factor and expense of peptide receptor radionuclide therapy

The PRRT service in this country has been a remarkable example of indigenization: at the start of our PRRT program, ^{177}Lu-DOTATATE PRRT at the Radiation Medicine Centre used to cost between Rs. 20,000 and 22,000. In 2019, the cost of one cycle of ^{177}Lu-DOTATATE PRRT at this center costs around Rs. 8000–10,000 with virtually all steps of production and radiolabeling procedures indigenized at the center. Thus, five cycles of PRRT are completed at a convenient and much affordable cost of Rs. 50,000 for a patient. Compared to this, the cost of the imported ^{177}Lu-DOTATATE per cycle would cost around Rs. 150,000/cycle (nearly 15 times more). We have been satisfied with the indigenous product which has produced excellent results in a large number of patients who underwent the treatment procedure at our institute.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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