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Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors

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Peptide receptor radionuclide therapy (PRRT), over the years, has evolved as an important modality in the therapeutic armamentarium of advanced, metastatic or inoperable, progressive Neuroendocrine Neoplasms (NENs). This review deliberates on the basic understanding and applied clinical aspects of PRRT in NENs, with special reference to (1) tumor biology and receptor characteristics, (2) molecular PET-CT imaging (in particular the invaluable role of dual-tracer PET with [^{68}Ga]-DOTA-TATE/NOC and [^{18}F]-FDG for exploring tumor biology in continuum and individualizing treatment decision making) and NEN theranostics, (3) relevant radiochemistry of different therapeutic radionuclides (both beta emitting ^{177}Lu-DOTATATE and ^{90}Y-DOTATATE and alpha emitting ^{225}Ac-DOTATATE), and (4) related dosimetric considerations. Successful clinical management of the NENs would require multifactorial considerations, and all the aforementioned points pertaining to the disease process and available logistics are key considerations for state-of-the-art clinical practice and delivering personalized care in this group of patients. Emphasis has been placed on relatively intriguing areas such as (1) NET grade 3 of WHO 2017 classification (ie, Ki-67>20% but well-differentiation features), (2) "Neoadjuvant PRRT," (3) combining chemotherapy and PRRT, (4) 'Sandwich Chemo-PRRT', (5) duo-PRRT and tandem PRRT, (6) resistant functioning disease with nuances in clinical management and how one can advocate PRRT rationally in such clinical settings and individualize the management in a patient specific manner. Relevant clinical management issues related to some difficult case scenarios, which the Nuclear Medicine attending physician should be aware of to run an efficient clinical PRRT services, are described.

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Introduction to PRRT: Factors Behind Its Remarkable Growth

Introduction

The last decade has witnessed a remarkable growth of somatostatin receptor (SSTR) receptor-based molecular targeted systemic radionuclide therapies (PRRT) as an important treatment modality in the clinical management of patients with advanced, metastatic or inoperable, progressive somatostatin receptor–positive neuroendocrine tumors (NETs) (Fig. 1). The beta-emitters such as Lutetium-177 (^{177}Lu) and Yttrium-90 (^{90}Y), radiolabeled in the radiopharmaceutical form as ^{177}Lu-DOTATATE and ^{90}Y-DOTA-TOC/TATE respectively have received regulatory approvals in multiple countries, and more recently alpha emitter Actinium-225 (radiolabeled as ^{225}Ac-DOTATATE) as an investigational agent, have been used for PRRT, though vast majority of the therapies till date have employed ^{177}Lu-DOTATATE owing to its favorable characteristics including well-tolerability and minimal adverse effects. The present treatise is an updated summary of clinical nuances of PRRT practice, the radiopharmaceutical aspects and the dosimetric considerations of this promising therapeutic approach.

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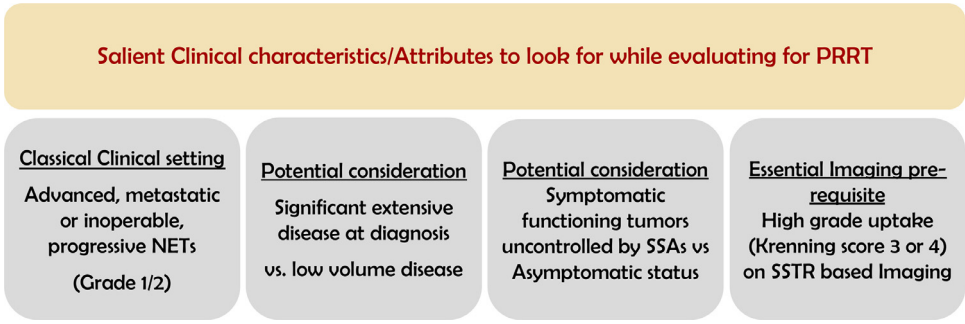

Figure 1 Salient clinical characteristics/attributes to look for while evaluating for PRRT.

Tumor Biology and Receptor Characteristics of the NENs: Comparison Between WHO 2010 and WHO 2017 Grading Classification System

The neuroendocrine neoplasms (NENs) represent widely heterogeneous group of tumors originating from the diffuse neuroendocrine system.[1] The Surveillance, Epidemiology, and End Results program registries showed the incidence rate of NETs increased by 6.4-fold from 1973 (1.09 per 100,000) to 2012 (6.98 per 100,000).[2] Over the past two decades, rapid advances in the understanding of the pathophysiology and molecular biology of NENs have led to improvements in the diagnosis and management of this group of patients with application of new personalized therapeutic strategies, based upon the biology of the tumor.

Salient distinctive points between WHO 2010 and 2017 grading classification systems: recognition of a distinctive subset "NET Grade 3" and its potential implication for PRRT

The 2010 WHO classification categorized the tumors as NET grade 1 (Ki-67: <3), NET grade 2 (Ki-67: 3-20), and NEC grade 3 (Ki-67: >20).[3] The first 2 grades correspond to well-differentiated tumors, which is pathologically defined by cells showing (1) minimal to moderate atypia, (2) absence of necrosis, and (3) diffuse and intense expression markers of neuroendocrine differentiation, that is, synaptophysin or chromogranin A. However, following this classification, there was a "gray zone" subset of 'morphologically well-differentiated NETs' with "high Ki-67 labeling index (LI)," these tumors with well-differentiated cellular characteristics may not be responsive to the chemotherapy regimen employed for poorly differentiated grade 3 NEC.

Recently, the common classification framework for neuroendocrine neoplasms across organ systems was proposed by the International Agency for Research on Cancer and World Health Organization (WHO) expert consensus with an aim to unify the approach and reduce confusion.[4] Furthermore, the ambiguity of Grade 3 NEC in the 2010 WHO Grading System[3] was addressed by the 2017 WHO Grading System,[4] which recognized the subset of "NET grade 3" with Ki-67 LI of >20.

It is imperative that patients with NETs that overexpress the SSTR2, are also the potential individuals for SSTR2 targeted therapies such as synthetic somatostatin analogs (SSAs) and radio-peptides or PRRT and have an improved prognosis[5] with these targeted therapies.

Conventional Therapy of NEN: Advantages of PRRT Vis-A-Vis Other Treatment Options

A number of therapeutic options exist for treating progressive metastatic/advanced NENs, these include: (1) cytoreductive surgery (when it is feasible), (2) SSAs such as octreotide and lanreotide (available as long acting and short acting formulations), (3) chemotherapy (combination of capecitabine-temozolomide, known as CAPTEM regimen or platinum-based regimen), (4) newer targeted agents available (everolimus and sunitinib), (5) locoregional ablative therapies such as (a) radiofrequency ablation, (b) selective hepatic transcatheter arterial embolization, (c) chemoembolization, (d) selective internal radiotherapy, and (e) laser-induced thermotherapy. The factors behind the increasing use and popularity of the PRRT are the following: (1) highly targeted nature of the treatment, (2) excellent tolerability of PRRT with minimal toxicity profile, and (3) convenient treatment scheduling of PRRT (completed in few discrete 1-day cycles at 10-12 weeks interval). These advantages stand out when compared vis-a-vis the other newer targeted agents, their associated adverse effects and the requirement to remain on these drugs until progression and of course, the cost associated with such regimen.[6]

Fundamental Principle of Clinical Application of Synthetic Somatostatin Analogues and PRRT in NENs and their mechanism of action

Somatostatin receptors and synthetic somatostatin analogues

SSTRs are a family of G-protein-coupled receptors comprising of five distinct subtypes (*SSTR1* to *SSTR5*). Signaling through

SST2 receptor inhibit hormone release and also causes antiproliferation, whereas stimulation of SST2 and 3 causes apoptosis; a role of anti-angiogenesis of somatostatin and somatostatin analogues has also been implicated. The effects of endogenous somatostatin are mediated through all 5 somatostatin receptors (ie, SSTR1-SSTR5), however, its half-life is 1-3 minutes due to the rapid degradation by peptidase enzymes present in the plasma and tissues. Thus for clinical use in NENs, exogenous formulations known as SSAs have been developed and employed: octreotide and lanreotide, 2 synthetic SSAs, bind primarily to SSTR2 and SSTR5.[7,8] Both of them are available in two formulations (based upon the duration of action): (1) octreotide is available as (i) an immediate-release injection (administered as subcutaneous injection, single ampoule containing 100 mcg; trade name: sandostatin/octride short-acting) and as (ii) a long-acting repeatable formulation (known as LAR Depot, injected intramuscularly intragluteally once every month, the recommended starting dose of 20 mg and dose titration in 10-mg increments) (trade name: Sandostatin/Octride LAR). (2) Lanreotide is available in (i) a *sustained release* formulation (trade name: "Somatuline LA," 30 mg), injected intramuscularly every 10-14 days, and (ii) an *extended release* formulation as acetate ("Somatuline Autogel"/ "Somatuline Depot," 60 mg, 90 mg or 120 mg), which is administered subcutaneously once a month.

Mechanism of action of SSA and clinical results

The SSAs have been traditionally used for treatment and control of secretory symptoms such as diarrhea and flushing associated with metastatic tumors in patients of NEN, where they inhibit the release of serotonin, gastrin, vasoactive intestinal peptide, and other hormones and their metabolites. The recent studies have also demonstrated their efficacy in inhibiting tumor growth. The postulated mechanism of action here are either by regulating the signaling pathways of tumor cell proliferation/apoptosis (direct effect) and angiogenesis (direct and indirect effect). The results of the phase III prospective, randomized "PROMID" study proved that octreotide LAR significantly prolonged the time to progression (14.3 months vs. 6 months with placebo) in patients with unresectable, well-differentiated metastatic midgut NETs,[9] while the CLARINET study with lanreotide undertaken in nonfunctional, metastatic GEP-NETs (with a Ki67 <10%) demonstrated the median progression-free survival (PFS) was not reached in the lanreotide group versus 18.0 months with the placebo group.[10]

Theranostics of PRRT in NENs and underlying principles including the radiobiology of major beta emitters

The proof-of-the-principle of this therapy is connected with that of "Theranostics" (ie, "*Treat what you see & See what you treat*"), defined by integration of a diagnostic testing (diagnostic modality: ^{68}Ga-DOTA-TOC/NOC/TATE for PET imaging or ^{99m}Tc-HYNIC-TOC SPECT, where the former not available) for the presence of a molecular target ($SSTR_2$), for which a specific treatment/drug is intended (mostly lutetium-octreotate or ^{177}Lu-DOTATATE).

In contrast to the SSAs, PRRT is a *radio*-peptide therapy that is molecular targeted and receptor-based, delivering targeted high dose of radiation directly to the neuroendocrine tumor cells and causing damage to the target cells. Among the 5 SSTRs, somatostatin receptor subtype 2 ($SSTR_2$) is primarily targeted by PRRT, in view of its overexpression and dominance in the NENs. The therapy is delivered in the form of an intravenously administered unsealed radiopharmaceutical. Following binding to the transmembrane $SSTR_2$ receptors of NET, the agent is actively transported into the cell via endocytosis, wherein it causes the desired double-strand DNA breakage and the resultant effect on the tumor cell damage. Bystander effects related cellular damage on the adjacent tumor cells has also been proposed. The most commonly used agent for PRRT world over is ^{177}Lu-DOTATATE (lutetium-DOTA-(Tyr^3)-octreotate or lutetium oxodotreotide). Yttrium-90 DOTATATE or DOTATOC is the other beta emitting alternative, in which the larger range of ^{90}Y (maximum tissue range ~11 mm) due to the higher beta particle energy [Eβmax = 2.28 MeV] makes it more suitable for larger tumors, while ^{177}Lu-DOTATATE demonstrates more efficacy and preferred for smaller tumors [Eβ(max) = 0.497 MeV; maximum tissue range ~2.5 mm].

[DOTA^0, Tyr^3]octreotate versus [DOTA^0,Tyr^3] octreotide: a treatise on the ligands for their application in PRRT

"DOTA-TATE" represents an amino acid peptide compound containing tyrosine^3-octreotate bonded covalently with a bifunctional chelator (DOTA or tetraxetan). Octreotate is a SSTR2 agonist that closely simulates octreotide, differing from the latter in that the C-terminal threoninol (an amino alcohol) is replaced by threonine in the former. The chemical modification confers ~ 9-fold enhancement in affinity of [DOTA 0, Tyr 3]octreotate in comparison to [DOTA 0,Tyr 3] octreotide for the receptor $SSTR_2$, the major target for the NENs. This translates, with regard to their radiolabeled counterparts, ~ 6-7-fold increase in affinity for $SSTR_2$ and finally results in ~4-5 times enhancement in the tumor uptake of the radiopharmaceutical and correspondingly enhanced radiation absorbed dose.[11]

A treatise on Radiopharmaceuticals Employed for PRRT: The Radiochemical Perspectives of ^{177}Lu/ ^{90}Y/^{225}Ac-Labeled Somatostatin Analogue Peptides

Radionuclides for PRRT using somatostatin analogue peptides

Selection of appropriate radionuclide is one of the key determinants for the effectiveness of PRRT using somatostatin (SST) analogs. Among various β^- emitting radionuclides explored in preclinical and clinical settings, ^{90}Y and ^{177}Lu are the most

Table 1 Characteristics of Key Radionuclides for PRRT Using Radiolabeled Somatostatin Analogs

Radionuclide	Half-Life	Emissions	Maximum Energy of Particulate Emission	Maximum Tissue Penetration Range	Source
^{90}Y	64.1 h	β^-	2284 keV	11 mm	^{90}Sr/^{90}Y generator
^{177}Lu	6.65 d	β^-, γ	497 keV	2.5 mm	Reactor
^{161}Tb	6.88 d	β^-, Auger e, γ	593 keV (β^-)	3 mm	Reactor
^{225}Ac	10.0 d	α, β^-, γ	5792 keV (α)	Few μm	Separation from ^{229}Th, decay product of ^{233}U

extensively used ones in clinical context.[12] Also ^{161}Tb is emerging as another potential candidate.[13] Apart from these, α particle emitter ^{225}Ac has been introduced in the targeted alpha therapy for gastroenteropancreatic neuroendocrine tumor.[14] The characteristics of these radionuclides given in Table 1.

Among the therapeutic radionuclides listed in Table 1, ^{90}Y [$T_{1/2}$ = 64.1 h, E_β(max) = 2284 keV, no γ photon] was the first one to be used clinically in PRRT with the SST analog peptides. [^{90}Y]Y-DOTA-Tyr^3-octreotide ([^{90}Y]Y-DOTATOC) has been extensively used in human patients.[15-18] However, there are 2 drawbacks which has restricted the broader utility of ^{90}Y in PRRT: (1) renal toxicity observed in patients due to high energy of β^- particles of ^{90}Y[11] and (2) issues related to availability of ^{90}Y in large scale. No-carrier-added (NCA) ^{90}Y suitable for use in PRRT is obtained from ^{90}Sr/^{90}Y radionuclide generator system. The parent radionuclide ^{90}Sr is one of the major fission products of ^{235}U and is radiochemically isolated in highly pure form from fission products.[12] The separation of NCA ^{90}Y suitable for human clinical utilization from ^{90}Sr is highly challenging owing to the strict regulatory requirement of very low permissible limit of ^{90}Sr in separated ^{90}Y. Strontium-90 in ionic form localizes in the skeleton and owing to its long half-life (28.8 y) is highly radiotoxic. Consequently, maximum permissible lifetime dose burden of ^{90}Sr for an adult is as low as 74 kBq.[12] These factors impose important restrictions on the commercial availability of clinical grade ^{90}Y in quantity that is required for its wide utility in PRRT.

Lutetium-177, although introduced at a later stage in PRRT using SST analogs as compared to ^{90}Y, has fast emerged as the most preferred choice due to its more favorable decay characteristics as well as large-scale availability in a suitable radiochemical form through straightforward production route.[19-21] Lutetium-177 decays to stable ^{177}Hf by emission of low to medium energy β^- particles [E_β(max) = 497 keV (78.6%), 384 keV (9.1%) and 176 keV (12.2%)]. It also emits few γ photons, 113 keV (6.4%) and 208 keV (11.0%) being the most prominent among them. This makes ^{177}Lu as one of most attractive choice for in vivo targeted therapy, particularly in case of small and metastatic tumors. Apart from the clinical advantages (enumerated earlier in details), another important aspect is the large-scale commercial availability of ^{177}Lu with very high radionuclidic purity and desired specific activity at an affordable cost. This is one aspect where ^{177}Lu has a distinct advantage over all other potent radionuclides which have either been used or proposed for PRRT using SST receptors.

In recent years, targeted α therapy (TAT) of SST receptor over-expressing malignancies is slowly emerging as a very efficacious treatment option and ^{225}Ac has been the radioisotope of choice.[14,22] Ac-225 decays with a half-life of 10 d following a complicated decay chain involving the emission of a number of α and β^- particles as shown Figure 2. The cytotoxic effect of ^{225}Ac has been reported to be very high owing to its longer half-life and number of alpha-particle emissions.[22] Despite these advantages, the practical drawback is very limited availability of this radioisotope. Presently, ^{225}Ac is made available in limited quantities by radiochemical separation from two ^{229}Th sources, one located at Oak Ridge National Laboratory (ORNL), USA and the other at the Institute for Transuranium Elements in Karlsruhe, Germany. Efforts are underway to produce the radioisotope using both high energy proton induced spallation of ^{232}Th as well as ^{226}Ra (p,2n) ^{225}Ac route using accelarators.[22]

Production strategies of ^{177}Lu in the nuclear reactor: direct and indirect routes, their relative merits and demerits

Two alternative strategies are available for production of ^{177}Lu with adequate specific activity required for its utility in PRRT. The first is the "direct" route which involves the

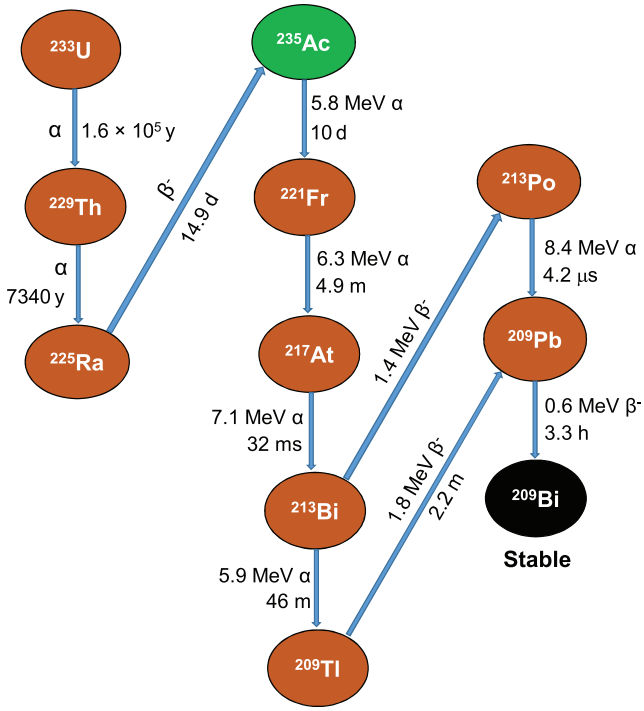

Figure 2 Decay chain of ^{233}U indicating production and decay of ^{225}Ac.

neutron activation of highly enriched (in ^{176}Lu) lutetium target [^{176}Lu(n,γ)^{177}Lu] in research reactors with medium to high thermal neutron flux.[19-21,23-28] The second route or the "indirect" route is based on neutron irradiation of highly enriched (in ^{177}Yb) ytterbium targets leading to the formation of NCA^{177}Lu from the β^- decay of the short-lived activation product ^{177}Yb ($T_{1/2}$ = 1.9 h). The post-irradiation radiochemical processing in the former case involves simple dissolution of the irradiated target, whereas the latter route involves elaborate procedure to separate ^{177}Lu from ytterbium targets as well as its radionuclides.

The indirect route of production offers two distinct advantages over the direct route, (1) it provides NCA ^{177}Lu (theoretical specific activity 4.03 TBq/mg, 109 Ci/mg), which in turn leads to higher specific activity of the radiolabeled peptide resulting in improved therapeutic efficacy,[29] (2) ^{177}Lu produced from indirect route is practically free form any radionuclide contaminant, provided a robust radiochemical separation strategy is adopted to separate ^{177}Lu from radionuclides of ytterbium. Different approaches have been explored for the separation of clinical grade NCA ^{177}Lu from bulk quantity of neutron irradiated ytterbium target.[26-28] However, despite these developments, the implicit need of a complex radiochemical separation procedure to isolate ^{177}Lu of requisite purity and recovery of expensive enriched ^{176}Yb are challenging. The second important aspect is the cost of production. It can be shown by theoretical calculation that irradiation of 1 mg of 99% enriched (in ^{176}Yb) Yb_2O_3 target at a thermal neutron flux of 5×10^{14} n/cm^2.s will produce only ~5.55 GBq (~150 mCi) of ^{177}Lu.

In contrast to any other medically useful radionuclides, direct (n,γ) route can be utilized for large-scale production ^{177}Lu with specific activity adequate for preparing receptor-specific therapeutic radiopharmaceuticals in nuclear reactors having medium to high thermal neutron flux (1.0×10^{14} n/cm^2.s or higher) using enriched lutetium target (80% or more in ^{176}Lu). This is possible due to the following two reasons, (1) ^{176}Lu has very high thermal neutron capture cross section (σ = 2090 b, I_0 = 1087 b) for formation of ^{177}Lu and (ii) neutron capture cross section of ^{176}Lu does not follow 1/v law and there is a strong resonance very close to the thermal region.[30] Consequently, it is possible to produce ^{177}Lu of specific activity of more than 740 GBq/mg in a medium flux reactor. The specific activity of ^{177}Lu can be augmented to 1850 GBq/mg or even higher by irradiation in high flux reactors[19,23] such as the high flux research reactor at the Oak Ridge National Laboratory and the SM3 reactor in Dimitrovgrad , The Russian Federation. The most significant advantage of direct route over the indirect route is the simplicity of post-irradiation chemical treatment procedure, which makes it much less technologically demanding as well as cost-effective compared to the other route. Moreover, there is absolutely no impediment towards scaling up the production as per its clinical requirement. On the contrary, the major concern in the large-scale clinical utilization of ^{177}Lu produced via the direct route is the presence of co-produced ^{177m}Lu, which creates problem in the disposal of radioactive wastes arising from the treatment of large number of patients beside the additional radiation dose burden to the patients. A careful optimization of the duration of irradiation depending on the available thermal neutron flux of the reactor is essential in the direct route to obtain ^{177}Lu in the highest achievable specific activity while keeping the contamination from ^{177m}Lu to minimum.[18-20,25,31]

Chemistry and radiochemistry of ^{177}Lu/^{90}Y/^{225}Ac relevant to formulation of radiopharmaceuticals for PRRT

In aqueous medium lutetium exists in highly stabilized +3 oxidation state (having stable electronic configuration of [Xe]4f^{14}) in the form of nine-coordinated aqua complex $[Lu(H_2O)_9]^{3+}$[19]. Electrons in the outermost 4f orbitals are incapable of bond formation since they are tightly bound due to high effective nuclear charge and are not influenced by ligands surrounding the metal ions. The ionic radius of Lu^{3+} (86 pm) is smallest among lanthanides.[19] Consequently, Lu^{3+} in acidic medium functions as hard acid and exhibit strong tendency to form complexes with hard donor atoms such as F^-, O, and N.[19] The coordination number is usually 8 or 9 which impart thermodynamic stability to the complex.[19] Numerous studies have shown that the macrocyclic polyaminophosphonic acid chelator DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) forms complex with Lu^{3+} with exceptionally high thermodynamic stability (Log K = 25.4 at 298 K).[32-34] Similarly, both Y^{3+} and Ac^{3+} also forms highly stabilized complexes with DOTA.[33-35] These complexes exhibit capped square antiprism geometry where the basal plane is occupied by four amine nitrogens of the macrocycle, the capped plane is occupied by four carboxylate oxygens, and the capping position is occupied by a water molecule (Fig. 3).

It is pertinent to mention that although the thermodynamic stability of [^{225}Ac]-Ac-DOTA complex has been reported to be high, the DOTA complexes of the initial daughter products of the ^{225}Ac radioactive decay chain, namely, ^{221}Fr ($T_{1/2}$ = 4.8 min) and ^{217}At ($T_{1/2}$ = 32 ms) are not so stable.[35] This is a cause of concern, as it may lead to dissociation of these daughter radionuclide from the DOTA-peptide complex in vivo and eventually increase radiation dose burden to healthy non-target organ, such as kidneys.

Formulation of [^{177}Lu]Lu-DOTA-peptide conjugate for PRRT using SST analogs using ^{177}Lu obtained from Indirect and Direct Routes

[^{177}Lu]Lu-DOTA^0-Tyr^3-octrotate ([^{177}Lu]Lu-DOTA-TATE, Fig. 4) is the most extensively used radiolabeled SST analog peptide. The radiopharmaceutical formulation (Lutathera) was approved by US FDA in 2018 for the treatment of somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumors. Prior to that, Lutathera was approved by European Medical Association in 2017. Advance Accelerator Applications (a Novartis company, Canada) currently holds the marketing rights of the

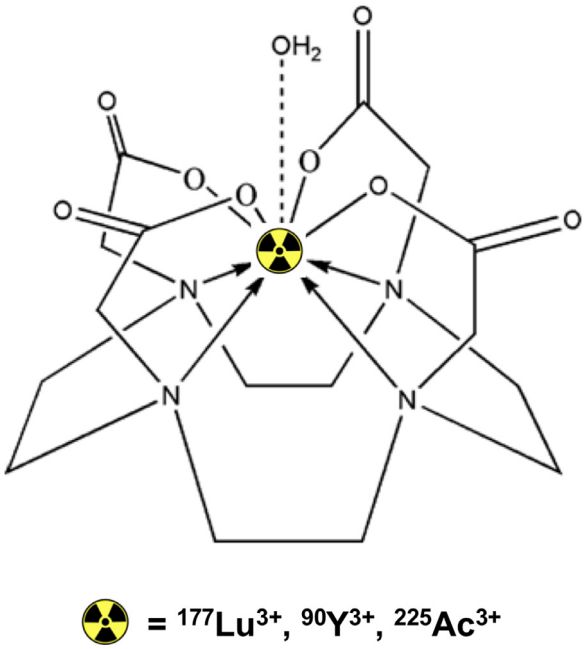

Figure 3 A representative structure of DOTA complex of $^{177}Lu^{3+}$, $^{90}Y^{3+}$, and $^{225}Ac^{3+}$.

radiopharmaceutical preparation. The radiopharmaceutical product [^{177}Lu]Lu-DOTA-TATE used most extensively is produced in a GMP (Good Manufacturing Practice)-compliant module by reacting NCA [^{177}Lu]$LuCl_3$ with DOTA-TATE under suitable conditions.[36] The finished product is generally available in ready-to-use single dosages containing 7.4 GBq ± 10% activity of ^{177}Lu and 100 μg (70 nmol) of DOTA-TATE, such that the specific activity of the radiolabeled product is ~ 106 GBq/μmol.[36]

Alternatively, [^{177}Lu]Lu-DOTA-TATE is formulated at hospital radiopharmacy or distributed from centralized radiopharmacy using moderate specific activity [^{177}Lu]$LuCl_3$ produced by direct neutron activation of isotopically enriched (80% or higher in ^{176}Lu) lutetium target. In this approach, the specific activity of ^{177}Lu used is usually more than 740 MBq/μg and amount of DOTA-TATE used is 2.0-2.5 times molar excess compared to that of Lu.[37] In India, generally, the second approach is utilized for formulation of [^{177}Lu]Lu-DOTA-TATE used for clinical use.[37]

Indigenous production of Clinical Grade ^{177}Lu through direct neutron activation route: the Indian perspective

In India, clinical grade ^{177}Lu used in PRRT is indigenously produced following direct route by irradiation of enriched lutetium target (82% ^{176}Lu) at a thermal neutron flux of ~1.5×10^{14} n/cm^{2}s. The targets are irradiated for a period of 14 days, which was arrived at after extensive optimization studies carried out both by theoretical calculations as well as by irradiating the target for different durations. While the yield of ^{177}Lu per mg of Lu target (82% ^{176}Lu) has been found to be 805 ± 23 GBq/mg, the specific activity was 1012 ± 26 GBq/mg at the end of irradiation (EOI). This enhancement of specific activity is an added advantage for ^{177}Lu towards its utilization in receptor specific therapeutic radiopharmaceuticals.

The impurity burden of ^{177m}Lu in ^{177}Lu produced in our case was found be ~0.015% at EOI and ~0.02% at 48 h post-EOI, when ^{177}Lu is generally used in the clinic. This implies that for each patient administered with 7.4 GBq dose of ^{177}Lu-labeled SST analogue peptide, the administered dose of ^{177m}Lu is ~1.48 MBq (40 μCi). The presence of ^{177m}Lu at this level is not a matter of serious concern from the point of view of radiation dose burden to the patients. However, the use of each GBq of ^{177}Lu will lead to the accumulation of ~200 kBq of radioactive waste of ^{177m}Lu to be disposed by following delay and decay approach.

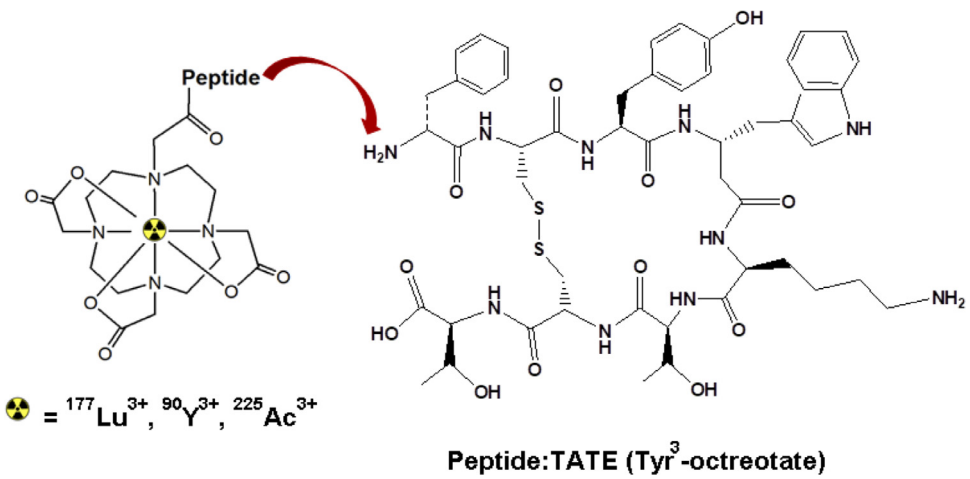

Figure 4 A representative structure of radiometal-labeled peptide conjugate DOTA^0-Tyr^3-octreotate (DOTA-TATE), where radiometal could be $^{177}Lu^{3+}$, ^{90}Y3+, and $^{225}Ac^3$.

Molecular PET-CT Imaging: The Valuable Adjunct Role of Dual-Tracer PET With [^{68}Ga]-DOTA-TATE/NOC and [^{18}F]-FDG for Exploring Tumor Biology in Continuum and Personalizing Treatment Strategies

Dual tracer PET-CT with ^{68}Ga-DOTATATE and FDG has evolved as an important imaging concept in the evaluation of metastatic NENs, before the treatment decision making.[6] The relative uptake of ^{68}Ga-DOTATATE/FDG in the lesions forms a valuable parameter for assessing the dynamic tumor biology in continuum and thus personalizing the treatment strategies.[6,38-40] Today, in most of the advanced centers, dual tracer PET-CT plays a valuable complimentary role alongside the tumor Ki-67/MIB-1 labeling index, that the attending physicians (both the medical oncologists and the Nuclear Medicine physicians) would like to look at before personalizing treatment strategies (such as SSA, PRRT vis-a-vis chemotherapy vis-a-vis chemo-PRRT) in NENs (Fig. 5).

Three specific clinical situations are enumerated below, wherein dual tracer PET-CT is particularly useful when compared to Ki-67/MIB-1 LI:

(i) *Deciphering the tumor biology in tumors with intermediate level of Ki-67 labeling index that is 10%-20%*: the relative uptake of ^{68}Ga-DOTATATE and FDG in the tumor gives an objective idea of the tumor biology.

(ii) *Tumors with Ki-67 LI between 20%-30%*: Dual tracer PET-CT plays important role and provides scientific basis for deciding between PRRT versus combined chemo-PRRT versus chemotherapy). As aforementioned, the WHO 2017 NET classification recognizes 2 different subsets within the grade 3 NETs, distinguishing well differentiated grade 3 neuroendocrine tumors (NET G3) from poorly differentiated grade 3 neuroendocrine carcinomas (NEC G3), which is important from management view-points.[5]

(iii) *Discordance between Ki-67 and the dual tracer PET-CT findings*: In a real-life scenario, this is not very infrequent; we must mention here that the Ki-67/MIB-1 labeling index being a singular number taken from a single lesion biopsy, is fraught with the shortcoming of its inability to assess the tumor biology as a whole on a continuous scale, particularly relevant in the borderline ranges. Additionally, the Ki-67 index of a biopsy specimen may not be representative of all the lesions or even the entire tumor, and such interlesional heterogeneity can be better depicted by the molecular PET-CT imaging.

Indications of PRRT: The Classical and Extended Indications

The classical clinical settings where PRRT is typically indicated include the following:

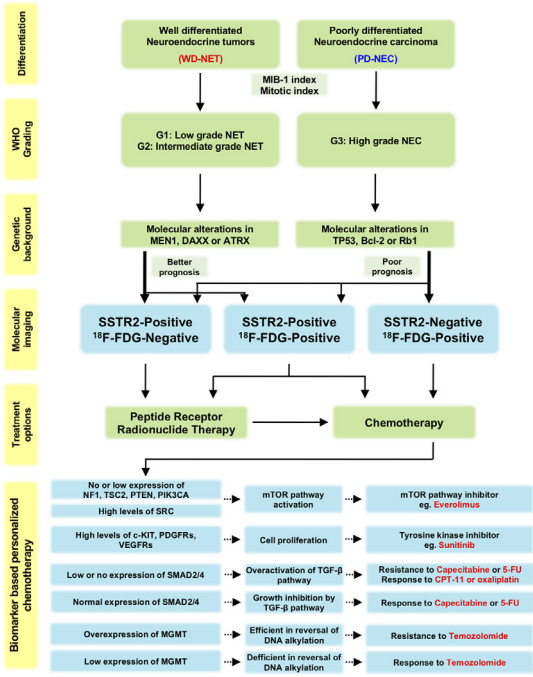

Figure 5 Schematic diagram illustrating inter-correlation between tumor classification and grade, histological parameters (Ki-67 or Mib1 index), genetic background, tumor proteomic characteristics, molecular imaging features, and the potential of the various therapeutic approaches in Neuroendocrine Neoplasms (Reproduced with permission from Basu et al[38]).

(a) "Advanced, metastatic or inoperable, progressive NETs" (traditionally grade 1 and grade 2), showing high uptake in the lesions on SSTR-based imaging.[41] While the usual setting has been disease progression on cold somatostatin analogues, PRRT has been increasingly considered upfront at diagnosis in patients with extensive/large-bulk disease on diagnostic study[6] (Fig. 1).
(b) We must mention here that though these patients typically encompass well-differentiated NENs of grade 1 or 2 as per the WHO 2017 classification, with Ki-67/MIB-1 labeling index up to 20%, there is increasing employment of PRRT in patients up to Ki-67 LI of 30% who demonstrate high uptake on SSTR based imaging (detailed further below), and included in some major guidelines recommendations (eg, ESMO guidelines).[42,43]
(c) Symptomatic functioning NETs, where the symptoms are not controlled by the long-acting SSAs (octreotide/lanreotide)
(d) High grade uptake (Krenning score 3 or 4) on SSTR-based ^{68}Ga-DOTA-TOC/TATE/NOC PET-CT or ^{99m}Tc-HYNIC-TOC SPECT-CT

Thus in the NET clinic, the attending physician needs to look *prima facie* for the 3 characteristics while deciding upon PRRT (Fig. 1).

Extended indications: "stretching the boundaries" (Adapted in part with modification from Basu et al[11])

The gratifying results, excellent tolerability with minimal side effects have encouraged PRRT to be adopted beyond the aforementioned classical indication. In multiple centers across the world, such "beyond the typical" indications have broadened the horizons of PRRT, including improving quality of life in a substantial fraction of these patients. In over a decade of experience with more than 4000 PRRTs successfully delivered in a large tertiary care setting in India, the clinical applications have been enlisted below:

(a) *PRRT in NENs with MIB-1 (Ki-67) labeling index 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.[5,42,43] Also, this group of tumors might demonstrate high uptake of FDG (on dual tracer PET-CT, where combined chemo-PRRT is now an available option with encouraging results (detailed later). As previously mentioned, the ESMO clinical practice guidelines for GEP-NENs advocates PRRT upto Ki-67 LI upto 30%.[42,43]
(b) *Beyond Gastroenteropancreatic NENs (GEP-NENs)*: While GEP-NENs have been the major and classical indications of PRRT, the 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 and include (in decreasing order of frequency):
  (i) metastatic/inoperable *Bronchopulmonary and Mediastinal/Thymic NENs*,[44,45]
  (ii) metastatic/inoperable *Medullary thyroid carcinoma***,[46]
  (iii) *Non-^{131}I-MIBG concentrating metastatic Paraganglioma & Pheochromocytoma*
  (iv) Non-iodine concentrating metastasis of differentiated thyroid carcinoma (TENIS: only 15%-20% of this patient subgroup demonstrates enough uptake to justify PRRT)**,[47]
  (v) Other tumors with neuroendocrine tumor differentiation/characterization: we have experience in metastatic *Merkel Cell carcinoma, Meningioma* and *recurrent/inoperable Phosphaturic Mesenchymal Tumor*.[48,49,50]

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.

Salient Points on Clinical Nuances Pertaining to PRRT Procedure

The patient preparation, the procedure proper and post-procedure follow-up for PRRT is relatively well-established and the readers are referred to the guidelines for this purpose.[41] Herein, we enumerate and discuss the clinical nuances that may be encounter by the attending physicians:

[a] *Variation in Treatment Schedules according to Clinical setting and Treatment Intent*: 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, though some variation exists between centers. At our center, the patients are managed with 2 different protocols: (1) *Neoadjuvant Intent Therapy*: A higher-end dose (ie, 200 mCi) is administered, with a short time interval (8 weeks between 2 cycles); (2) *Metastatic setting*: A mean of 150 mCi per cycle is administered at 12 weekly intervals. On an average, a patient receives 5 cycles in this protocol.

[b] *Renal Toxicity in PRRT*: One documented dose-limiting toxicity of PRRT has been renal toxicity at higher doses, due to the uptake of the radiopharmaceutical in the proximal tubule cells through megalin/cubilin system. Two aspects will be worth discussing at this point:

(i) *Variation in incidence of Nephrotoxicity between ^{90}Y-DOTA-TOC and ^{177}Lu-DOTATATE:*

The initial studies with PRRT documented significant permanent renal toxicity primarily as they were conducted with [^{90}Y]Lu-DOTA-TOC; the value from a Swiss study in over

1,000 patients treated with [^{90}Y]Lu-DOTA-TOC reported to be 9%.[51] With ^{177}Lu-DOTATATE, however, the incidence is substantially reduced,[52] which is an important reason why ^{177}Lu-DOTATATE has been adopted in most PRRT centers across the world. We observed excellent safety profile of ^{177}Lu-DOTATATE, including patients with single functioning kidney.[53,54] The molecular explanation for this difference is elucidated later.

(ii) *The role of pharmaceutical grade mixed amino acid formulations in case of non-availability of basic amino acid mixture*:

Pharmaceutical grade mixed amino acid has been used by many centers for renal protection in case of non-availability of basic amino acid (Lys-Arg): this has worked well. The individual centers should titrate the formulations being used so as to closely simulate the suggested combination of 25 g of lysine plus 25 g of arginine. Typically in our setting, renal protection is carried out with a mixed amino-acid infusion (6 bottles of 200 mL each, a total of 1200 mL), with the first 200 mL infused prior to the [^{177}Lu]Lu-DOTA-TATE administration of the treatment, soon after the administration of antiemetics.

[c] *Antiemetic Protocol: Combined ondansetron-dexamethasone and Aprepitant*

The emesis during PRRT is primarily due to the metabolic acidosis related to co-infusion of the positively charged amino acids (administered to competitively block the megalin-cubilin pathway-based proximal renal tubular reabsorption of the radiopeptide). In our experience, intravenous dexamethasone and ondansetron is effective in most cases and in our setting is a clinical routine before starting the amino acid infusion.[55] In patients where vomiting is uncontrolled by the ondansetron-dexamethasone combination, oral aprepitant, an NK_1 antagonist in the central and peripheral nervous system and acts by blocking substance P landing, is administered. The standard adult dose is 125 mg, 80 mg and 80 mg on days 1, 2, and 3, respectively.

In our center, if we observe the requirement of aprepitant during the first cycle of PRRT, we routinely advocate it from second cycle onward for the particular patient.

[d] *MinimizingAcute Syndrome in the post-treatment period*

Though PRRT is generally well tolerated with minimal acute side effects, there exists a rare risk of acute precipitation of carcinoid syndrome ("carcinoid crisis"), which could be life-threatening and needs emergency management. This phenomenon occurs due to sudden hormone release following PRRT and is more likely in patients with (1) large volume hepatic metastases and (2) poorly controlled functioning NENs. In our experience in a large volume of cases handled over the years, (1) priming the former group with cyproheptadine from 1 to 2 days before scheduled PRRT helps: we have adopted this practice on a regular basis (antiserotonergic effects: a potent antagonist of the 5-HT_2 receptors, which is the reason for its effectiveness in the treatment of serotonin syndrome).[55] (2) For patients with highly symptomatic functioning NENs, we advocate short acting octreotide injections (subcutaneous) till 1 day before of PRRT and start back next day following PRRT and continued till 10-14 days after therapy, which mostly takes care in preventing an acute syndrome.[55]

[e] *Patients with Poor Nutrition Status and anasarca:*

In a subset of patients with poor nutritional status and generalized anasarca, administering PRRT in isolation ward can be challenging. This is particularly more relevant to the developing world and is further compounded by the tryptophan loss, gastrointestinal loss of protein, and liver metastases leading to hepatic dysfunction. Aggressive oral protein supplementation in this group of patients, along with octreotide therapy before PRRT, enhances the general condition and increases the number of patients who can undergo PRRT uneventfully.[55]

Efficacy-Results in Metastatic Gastroenteropancreatic NENs (GEP-NENs)

While PRRT has been employed for metastatic NENs of various locations and other tumors of neuroendocrine characteristics,[46-50,56-60] metastatic Gastroenteropancreatic NENs (GEP-NENs) form the most common indication where this treatment is advocated and is reviewed in this treatise.

Response assessment parameters and results in various studies

The efficacy of PRRT is assessed in 3 scales: (1) Symptomatic response and improvement in health related quality of life (HRQoL), (2) biochemical response in terms of reduction/increase in tumor markers (serum CgA, 24 hours urinary 5-HIAA levels) and (3) imaging response (by RECIST and PERCIST scales). Amongst the 3 parameters, the most gratifying result is obtained in the form of remarkable symptomatic improvement and better quality of life (including those with functioning disease uncontrolled with SSAs such as long-acting octreotide/lanreotide). While the % documented varied slightly in between, most register an improvement in greater 80%; in our setting, we observed a symptomatic improvement in 90% of patients.[58] The next is biochemical response in terms of reduction of serum CgA/urinary 5-HIAA which is documented in around 60%-70% of patients. On imaging, partial objective responses is seen in around 30% of patients (complete response in 2%-6%) (Fig. 6). Additionally, stable disease is documented on imaging (either RECIST or PERCIST scale assessment) in around 60% who had otherwise demonstrated progressive disease on octreotide or lanreotide. In most studies, stable disease on imaging is also considered as "responders," thus along with "partial and complete response", the "responders" would vary between 70% and 80% following PRRT.

There are however specific clinical subsets (such as FDG avid disease), where the efficacy of PRRT alone is not satisfactory and chemo-PRRT is adopted in this subgroup (detailed below under "specific clinical situations")

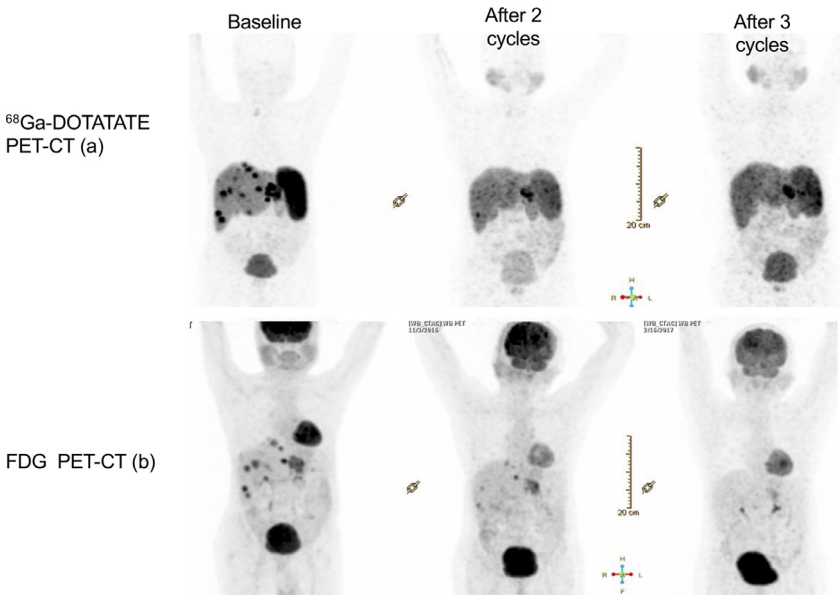

Figure 6 Excellent response obtained with [^{177}Lu]Lu-DOTA-TATE PRRT in a 70-year-old male, diagnosed as primary NET of body and tail of pancreas with multiple hepatic metastasis, MIB-1 index: 12% and no previous surgical intervention. Dual tracer PET-CT ^{68}Ga-DOTATATE PET (a) and FDG-PET (b) demonstrating Krenning grade IV uptake on baseline ^{68}Ga-DOTATATE PET (upper-left image) with relatively low-grade FDG (lower-left image). Following 3 cycles of [^{177}Lu]Lu-DOTA-TATE PRRT, the metastatic lesion in both scans show excellent response while the primary tumor shows partial response which was then considered for surgery (Reproduced with permission from Basu et al[11]).

Clinical outcome parameters: progression-free survival and overall survival

In addition to response assessment through aforementioned 3 parameters, the parameters that are measured as "outcome parameters" are (1) PFS, and (2) Overall survival (OS).

The phase III multicenter 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. The investigators concluded that PRRT appears to be substantially superior to other systemic treatment modalities available for metastatic NENs.[52] In a retrospective analysis in 1048 patients with neuroendocrine neoplasms, the overall survival obtained was 51 months (47.0-54.9).[61]

Specific Clinical Settings:

[1] "Sandwich" Chemo-PRRT Regimen in NENs with high ^{68}Ga-DOTATATE and ^{18}F-FDG uptake on dual tracer PET/CT

Metastatic NENs with lesions demonstrating both high ^{68}Ga-DOTATATE and ^{18}F-FDG uptake on dual tracer PET/CT forms a specific subset of tumors that can be effectively treated with a combination of PRRT and chemotherapy. Thus in NEN spectrum, one can subdivide the tumors in 3 specific subgroups based upon the dual tracer PET-CT results:

(i) Those with low Ki-67 index, which are usually positive on SSTR imaging with low/absent FDG uptake: they are treated with SSA and PRRT,

(ii) Those with high Ki-67 index, are usually negative on SSTR-based imaging and shows high uptake on FDG-PET: are treated with chemotherapy (CAPTEM if Ki-67 < 55% or platinum-based chemotherapy if Ki-67 > 55%).

(iii) An intermediate grey zone exists between the aforementioned two groups with the tumor demonstrating both high ^{68}Ga-DOTATATE and ^{18}F-FDG uptake on dual tracer PET/CT: herein a combined approach of PRRT plus chemotherapy appears a logical & rational approach.[62,63] In this regimen, 2 cycles of CAPTEM chemotherapy is sandwiched between 2 PRRT cycles of [^{177}Lu]Lu-DOTA-TATE. Thus, a typical schedule is PRRT followed by 2 cycles of CAPTEM followed by PRRT. In our set-up standard CAPTEM regimen comprising of oral capecitabine (CAP), 750 mg/m^2 twice daily for 14 days (D1−D14) and oral temozolomide (TEM) 200 mg/m^2 once daily for 5 days (D10−D14) followed by two weeks rest period and another CAPTEM cycle given for total 28 days is followed by next cycle of PRRT at around 3 months (Fig. 7). 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 'Chemo-PRRT' procedure was well tolerated in all patients with no grade III/IV hematological and renal toxicity in any of these 38 patients. (Fig. 8)

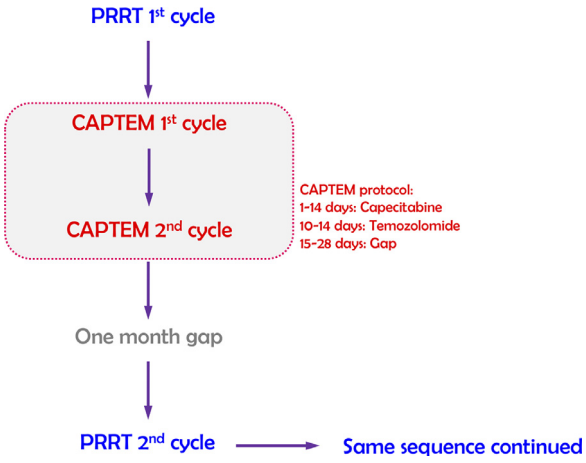

Figure 7 Treatment Protocol for "Sandwich Chemo-PRRT" *in* ^{68}*Ga-DOTATATE and FDG avid disease* in metastatic and advanced Neuroendocrine Neoplasms.

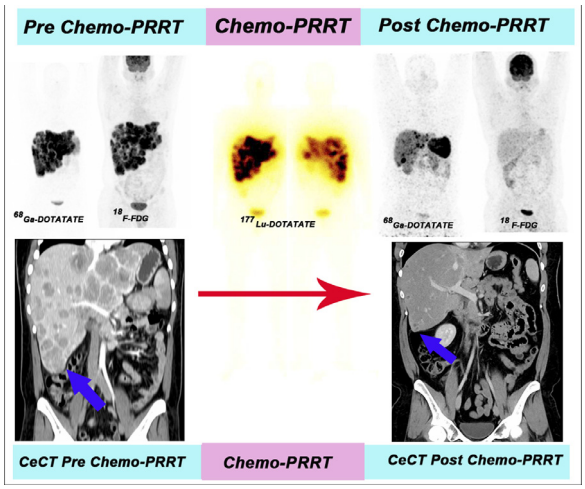

Figure 8 *Efficacy of Sandwich Chemo-PRRT in* ^{68}*Ga-DOTATATE and FDG avid large volume disease*. Excellent response (both by RECIST and PERCIST) to "Sandwich Chemo-PRRT" (Cumulative dose of 800 mCi of ^{177}Lu-DOTATATE, 12 cycles CAPTEM) in a patient of pancreatic NET with liver metastases, the post Chemo-PRRT images demonstrating significant reduction in size, number and SSTR uptake of liver lesions and complete resolution of FDG uptake in the lesions.

Uncommon subset of interorgan heterogeneity on dual tracer PET

Another area where the combined chemo-PRRT therapeutic strategy would be rational is in the presence of inter-organ heterogeneity on dual tracer PET (^{68}Ga-DOTATATE/^{18}FDG) in the same individual. We observed this in a very small fraction of patients (most of cases are Grade 1 or 2), where the dual tracer comparative PET-CT scan illustrate the phenomenon distinctively: herein, the ^{68}Ga-DOTATATE avid lesions to be targeted by PRRT while FDG avid lesions theoretically would be more amenable to chemotherapy (Fig. 9).

[2] Peptide receptor chemoradionuclide therapy (PRCRT) with concurrent 5FU chemotherapy:

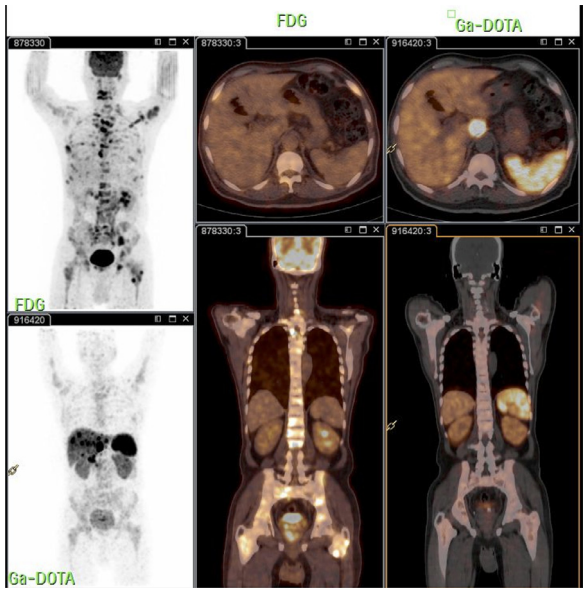

Figure 9 *Interorgan Heterogeneity in the same individual on Dual tracer PET-CT: Combined therapeutic Strategy?* Dual tracer PET (^{68}Ga-DOTATATE/^{18}FDG) imaging findings in a 65-year-old male, a diagnosed case of grade I duodenal NET with liver and skeletal metastases (duodenal polyp biopsy was suggestive of well differentiated NET with Mib1 LI <2%) is illustrated. The ^{68}Ga-DOTATATE PET-CT demonstrated high uptake in the hepatic metastases (Krenning score 4), there was faint uptake noted in the bone marrow (Krenning score 1). On FDG-PET/CT, the liver lesions did not demonstrate an appreciable focal uptake while the bone marrow lesions were distinctly positive with irregularly increased uptake throughout the axial and proximal appendicular skeletal marrow. (Reproduced with permission from Basu et al[62]).

PRCRT using ^{177}Lu-octreotate with concomitant 5-FU radiosensitizing infusional chemotherapy has been one regimen that has been investigated in patients with FDG-avid NET with good success, with long progression-free survival of 48 months in a cohort of 52 patients. The dosage of 5-FU in PRCRT in this regimen has been (200 mg/m^2/24 h), starting approximately 4 days before the day of PRRT administration, and continued for 3 weeks in total and early discontinuation in the event of hand–foot syndrome or other acute toxicity.[63,64]

[3] Neoadjuvant PRRT:

PRRT in the neoadjuvant setting has been examined by few groups for its ability to reduce the size of primary GEP-NENs to the point where an initially unresectable tumor becomes operable and have met with modest success.[65,66] In one analysis of the published results, the success for operability is around one-third of treated patients (~30%). This roughly equates with the proportion of partial response obtained with PRRT.

At our set-up, the inoperable disease became operable in around 26% patients in a population of 57 patients following PRRT (unpublished data) (Fig. 10). The PRRT was well tolerated in all 57 without any major hematologic or renal toxicity in any of these patients. We believe, this area needs further exploration and innovation, including possibility of combination therapy.

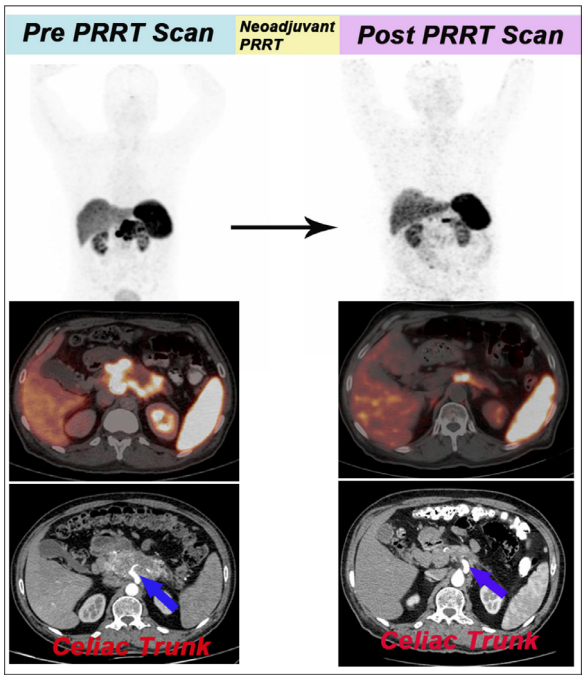

Figure 10 *PRRT in Neoadjuvant Setting.* A patient with locally advanced Pancreatic NET, MiB-1 LI=5%, Pre-PRRT scan shows complete encasement (more than 180°) of celiac trunk by ^{68}Ga-DOTA-TATE avid pancreatic lesion (SUVmax 80, 7.0 × 6.6 cm). The patient received neoadjuvant PRRT (cumulative dose of 850 mCi). Post PRRT ^{68}Ga-DOTATATE PET-CT showed significant reduction in size and SSTR uptake (SUVmax 30, 2.0 × 1.5 cm) of the pancreatic lesion with less than 180 ° encasement of celiac trunk.

[4] Duo-PRRT and Tandem PRRT:

[^{90}Y]Y-DOTA-TOC/TATE in combination with [^{177}Lu]Lu-DOTA-TATE has been tried by multiple groups, with an intent of balancing the advantages and adverse effects of both radionuclides viz. (1) superior efficacy of [^{90}Y]Y-DOTATATE for larger tumors due to higher beta-particle energy of 2.28 MeV (mean energy of 0.94 MeV) of ^{90}Y (maximum soft tissue range 11 mm) compared to that of ^{177}Lu [Eβ(max) of 497 keV (78% abundance), maximum soft tissue range 2.5 mm], and on the other hand, reducing the renal toxicity that has been documented more with ^{90}Yttrium-based PRRT due to the higher absorbed energy to normal kidneys. Thus, in these respects, ^{90}Y and ^{177}Lu can be complimentary to each other in that ^{90}Y is more suitable for larger lesions, while ^{177}Lu is most useful in eradicating smaller lesions (with the additional advantages of imageable gamma photons facilitating convenient post-therapy imaging and dosimetry).

Hence, a logical approach would be combining the two radionuclides, which can be undertaken in 2 ways:

(a) *Duo-PRRT*: [^{177}Lu]Lu-DOTA-TATE sequenced with [^{90}Y]Y-DOTA-TOC/TATE.[61,67,68] The algorithm and an example followed at our Institute is depicted in (Figs. 11 and 12)

(b) *Tandem PRRT*: Combined 1:1 ^{90}Y/^{177}Lu-DOTATATE administration simultaneously.[69,70]

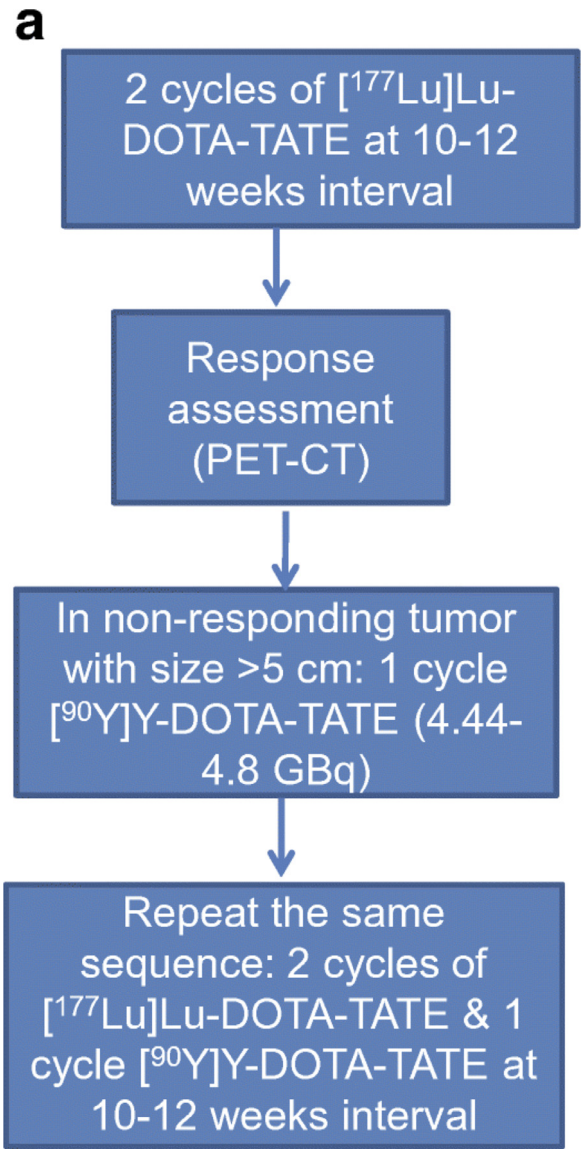

Figure 11 Treatment Protocol for "duo-PRRT" protocol for large volume *disease* (lesion size > 5 cm) in metastatic and advanced Neuroendocrine Neoplasms. (Reproduced with permission from Basu et al[68]).

Though the high efficacy and safety of both these approaches have been reported, further data need to be accrued as to how these approaches can be integrated in the treatment algorithm rationally.

[5] Resistant Functioning NEN with carcinoid syndrome:

In the practice of PRRT, this is one particular group that would require dedicated clinical attention for effective management of symptoms that has potential implications for health-related quality of life of the patients. While PRRT is very effective in controlling symptoms of carcinoid syndrome in functioning NENs that are otherwise resistant to conventional therapies (eg, octreotide/lanreotide)[71] (Fig. 13), the effect may not be apparent till the initial 2-3 cycles. During this period they would need, in a patient specific individualized manner, varying combinations of long acting and short acting octreotide in the interim months between the PRRT cycles (long acting formulation intramuscularly) and in the

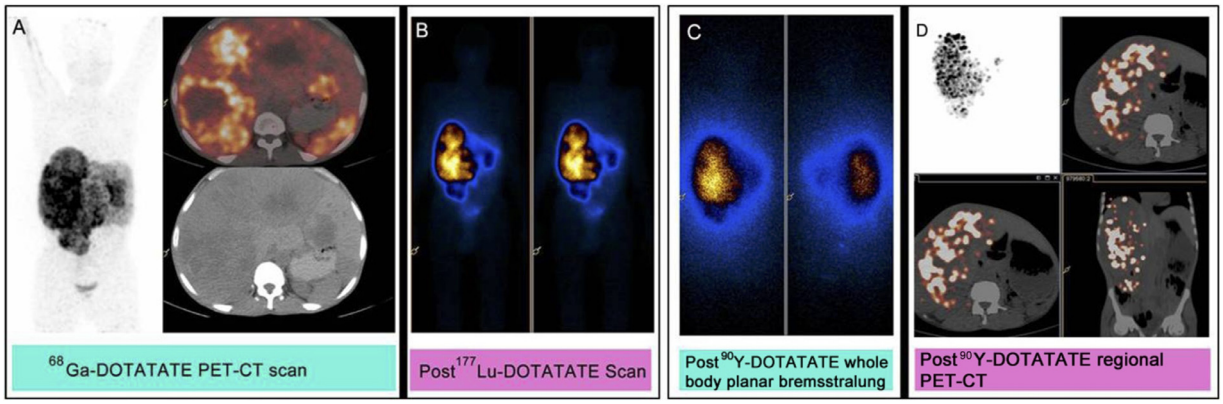

Figure 12 A 62-year-old male, known case of pancreatic NET with bulky metastatic liver lesions (initially treated with injection octreotide LAR) was considered for duo-PRRT protocol in view of large volume hepatic metastases, which was stable following ^{177}Lu-DOTATATE PRRT on imaging with worsening clinical symptoms. ^{68}Ga-DOTATATE PET-CT scan (Fig. 9A) showed intensely SSTR avid (Krenning score=4) multiple enlarge lesions in both lobes of liver and the last ^{177}Lu-DOTATATE post-therapy scan (Fig. 9B) showed good tracer uptake in liver lesions. Post ^{90}Y-DOTATATE whole body planar Bremsstrahlung imaging (Fig. 9C) and post ^{90}Y-DOTATATE regional PET-CT scan (Fig. 9D) demonstrated good tracer uptake of ^{90}Y-DOTATATE in liver lesions. Thereafter patient received ^{90}Y-DOTATATE therapy (single cycle, dose = 3.4 GBq). Post ^{90}Y-DOTATATE PRRT, patient showed improvement in symptoms without any acute adverse events.

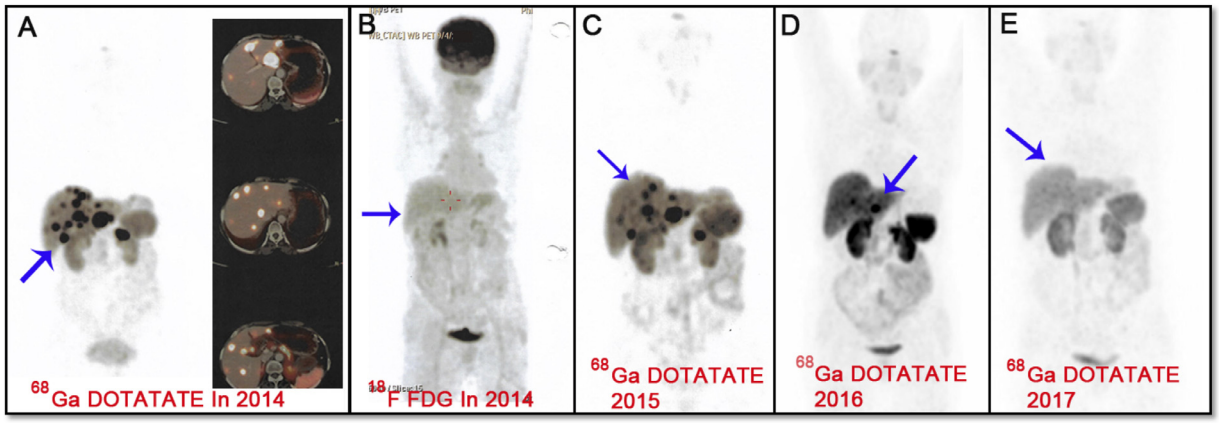

Figure 13 *Octreotide LAR non-responding functioning NET disease: excellent response to PRRT.* A patient of NET Grade 1 (primary: pancreatic tail) with hepatic metastases with functioning disease not responding to octreotide LAR (persistence of flushing +diarrhea− 10-12 times / day). [^{68}Ga]Ga-DOTATATE (A) and FDG PET/CT (B) at the time of baseline evaluation in 2014 showed SSTR avid pancreatic tail and multiple liver lesions, with no FDG uptake (consistent with grade 1 disease). Then patient received 4 cycles of PRRT with ^{177}Lu-DOTATATE (550 mCi), subsequent [^{68}Ga] Ga-DOTATATE scans (C-D) in 2015 and 2016 show significantly decrease SSTR uptake and size of liver lesions. In Dec 2017, [^{68}Ga]Ga-DOTATATE study showed complete resolution of liver lesions both structurally and also functional imaging, the patient becoming asymptomatic of the presenting complaints and significantly reduced serum CgA level.

last month prior to therapy, they would require management with short acting formulations of SSAs, which can be continued till 1 day prior to a ^{68}Ga-DOTATATE scan or PRRT. As previously mentioned, some of these highly symptomatic patients are started back on short acting octreotide next day following PRRT and continued till 10-14 days after therapy. Also, priming with an antiserotonergic agent (eg, Cyproheptadine) can be quite effective, that is routinely adopted in our set-up.

[6] Observation on increase in uptake on [^{68}Ga]Ga-DOTATATE PET-CT following CAPTEM chemotherapy or everolimus therapy in Metastatic Neuroendocrine Tumors with intermediate MiB-1 index having minimal lesional uptake on baseline: potential for feasibility of PRRT

In our practice, we have encountered NETs with intermediate Ki-67 LI showed minimal uptake SSTR-based study at baseline evaluation, rendering them unsuitable for PRRT initially. A fraction of such cases, when followed up following

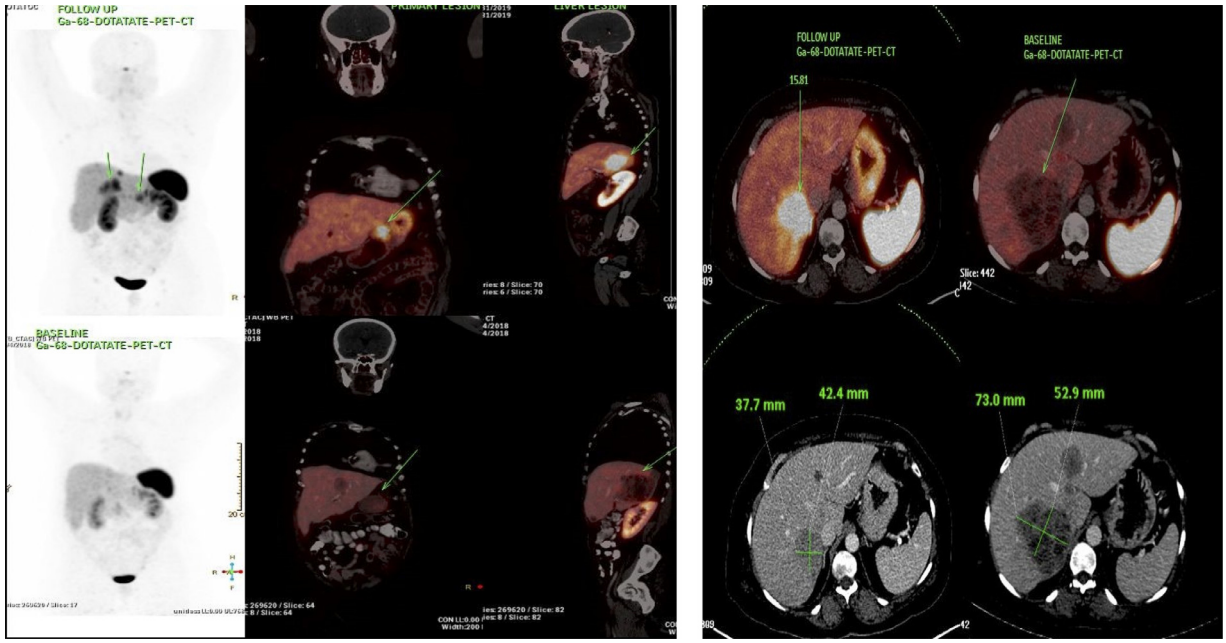

Figure 14 Baseline (lower panel) and follow-up (upper panel) [^{68}Ga]Ga-DOTATATE PET-CT following 6 cycles of CAPTEM chemotherapy: the maximum intensity projection (MIP), coronal, sagittal and transaxial images (right image) demonstrating enhanced tracer uptake in the follow-up study (the lesions are reduced in size as seen in CT images). (Reproduced with permission from Sharma et al[73]).

chemotherapy (such as capecitabine-temozolomide/CAPTEM or everolimus), have shown enhancement of tracer uptake on [^{68}Ga]Ga-DOTATATE PET-CT with high grade positivity making them potential candidates for PRRT in the course of disease. The existing literature is limited on this topic of chemotherapy induced enhanced uptake on SSTR-based PET imaging, with only two communications till date[72,73] and needs to be examined further (Fig. 14).

Dosimetric Considerations During PRRT

The dose limiting organs in PRRT are usually kidneys or the bone marrow.[74,75] When considering the maximum safe dose of 23 Gy to the kidney and 2 Gy to the bone marrow, Sandstrom et al[5] found that in 98.5 % cases the kidney is the dose limiting organ while only 1.5% cases bone marrow is the dose limiting organ. Since, radiolabeled somatostatin analogues are reabsorbed in the renal proximal tubules of the kidney, co-infusion of positively charged amino acids is undertaken from 30 minutes before and up to 4-6 hours after administration of radioactivity to protect the reabsorption. This will reduce the absorbed dose to the kidney by a mean of 47 % (range: 34%-59%).[76] Personalized dosimetry has been advocated by investigators with an aim to improve the outcome of PRRT and increase the survival of patients.[76-81] The doses estimated to kidney, liver, spleen, red marrow, whole body and tumors from ^{177}Lu-DOTATATE are presented in Table 2 (an illustrative example of dosimetry for calculating tumor absorbed doses is depicted in Fig. 15).

Table 2 Comparison of ^{177}Lu-DOTATATE Dosimetry Data Available in Literature and Our Study

Absorbed dose (mGy/MBq)						
Kidney	**Liver**	**Spleen**	**Bone Marrow**	**Total Body**	**Tumors**	**References**
0.9 ± 0.3	-	1.2 ± 0.5	0.04 ± 0.02	0.05 ± 0.02	9.7 ± 12.4	9
0.55 ± 0.20	-	-	0.046 ± 0.033	-	4.2 ± 2.9	8
0.57 ± 0.09	0.27 ± 0.05	1.17 ± 0.14	-	-	3.41 ± 0.68	10
0.88	0.21	2.15	0.07	-	-	7
1.15 ± 0.29	-	-	-	0.07 ± 0.02	6.7*	11
0.61	0.38	0.72	0.03	-	-	5
1.04 ± 0.03	1.00 ± 0.01	1.011 ± 0.129	-	-	-	4
0.63 ± 0.20	-	-	-	-	-	12
0.72 ± 0.23	0.13 ± 0.7	1.19 ± 0.58	0.041 ± 0.021	0.071 ± 0.025	8.83 ± 7.18	Our study@

*Median dose; @Study is in progress

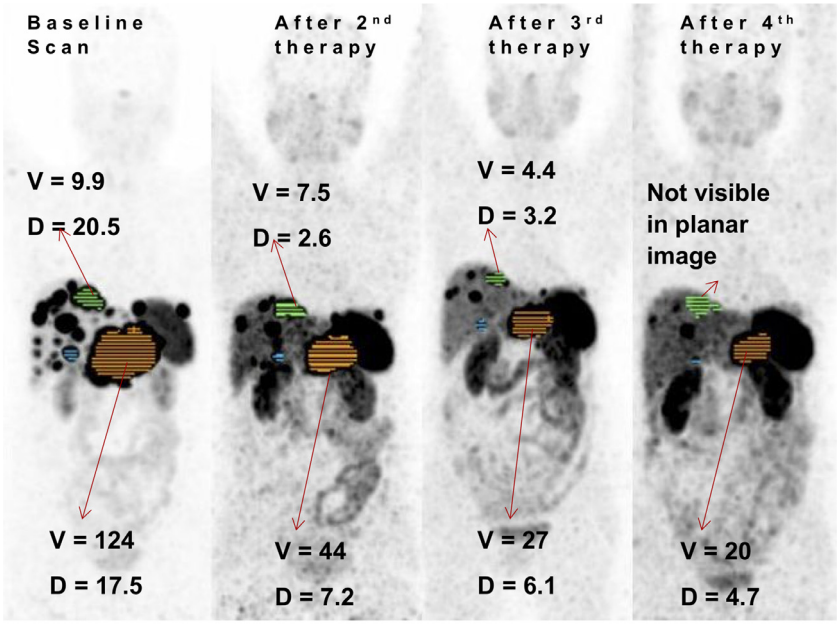

Figure 15 Comparative illustrations of tumor absorbed doses in a patient of metastatic NEN with responding disease following different therapy cycles of ^{177}Lu-DOTATATE PRRT.

Since ^{90}Y is a pure beta emitter, for dosimetry studies either ^{111}In-DTPA-TOC or ^{86}Y-DOTATOC (positron emitter) has been used as surrogate for ^{90}Y-DOTATOC on the basis of the hypothesis that their in-vivo behavior is similar. The doses estimates of ^{90}Y-DOTATOC to kidney, liver, spleen, red marrow, and tumors from ^{177}Lu-DOTATATE are presented in Table 3.

In case of targeted alpha therapy either ^{225}Ac or ^{213}Bi are labelled with DOTATOC, however dosimetric data are very sparse and of preliminary nature in the peer-reviewed literature with these two agents. Based on dosimetric study, the maximum tolerable dose of a single cycle ^{225}Ac-DOTATOC was found to be 40 MBq. In case of multiple fractions, it is 25 MBq every 4 months or 18.5 MBq every 2 months. In the aforementioned study, cumulative activities of 75 MBq were found tolerable with respect to delayed toxicity.[82]

The Challenges of NEN Management and Conceptualizing Future Approaches and Effective Treatment Strategies

The challenges of NEN management today are the fraction of patients that frequently demonstrate progressive disease; they can be classified into two groups (Fig. 16):

(a) Biology driven challenges: These are tumors with FDG avid disease
(b) Size driven challenges: Large volume tumors

The first one has been approached with combined chemo-PRRT (in our experience the "sandwich chemo-PRRT"

Table 3 Comparison of [^{90}Y]Lu-DOTA-TOC Dosimetry Data Available in Literature

Absorbed dose (mGy/MBq)					
Kidney	**Liver**	**Spleen**	**Bone Marrow**	**Tumor**	**References**
6.05	0.27	5.36			13
3.3 ± 2.2	0.7 ± 0.6	7.6 ± 6.3	0.03 ± 0.01	10.1	14
2.05	-	-	-	-	15
1.62 ± 0.53	-	-	-	-	16

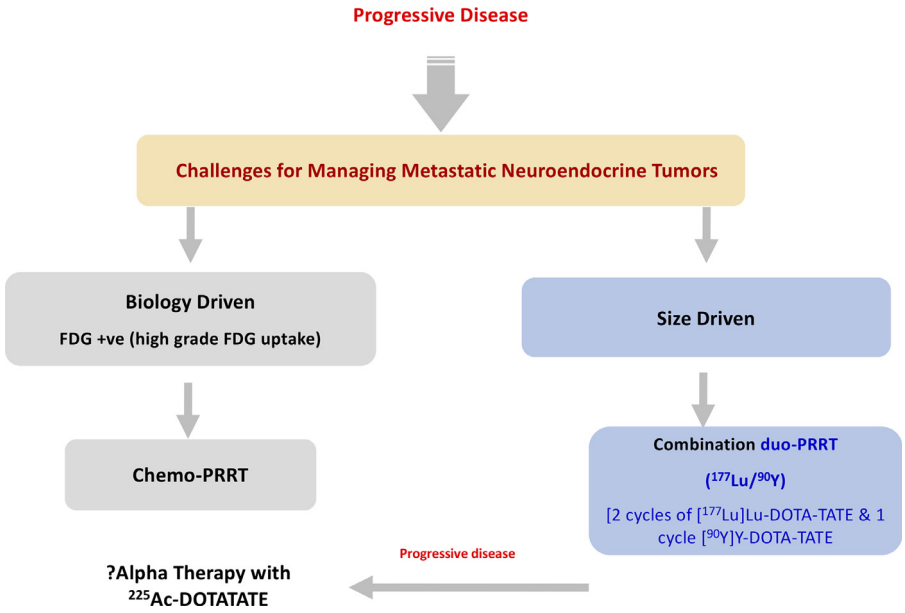

Figure 16 The challenges of metastatic NEN management and conceptualizing future approaches and effective treatment strategies.

approach has produced remarkable results The second group can be approached with either "duo-PRRT" or "tandem-PRRT" approach with a combination-sequencing or simultaneous administration of ^{177}Lu-DOTATATE and ^{90}Y-DOTATATE. The place of Alpha Therapy with ^{225}Ac-DOTATATE is evolving at this point and is likely to be adopted in the resistant progressive group of tumors.

Conclusion

Thus, the present communication on PRRT portrayed the multidimensional aspects of PRRT, with an aim to put together all salient points encompassing the clinical nuances, radiopharmaceutical aspects and the dosimetric considerations that would provide insights into this very promising treatment in metastatic/advanced GEP-NENs and other neuroendocrine tumors and adopt it in a rational manner. The challenges and the future potential of combination regimens has been outlined, which need to be examined further for enhancing the outcome in challenging and progressive resistant cases that cannot be addressed by the PRRT alone.

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