The College of Nuclear Physicians of South Africa Practice Guidelines on Peptide Receptor Radionuclide Therapy in Neuroendocrine Tumours

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Background: Peptide receptor radionuclide therapy (PRRT) for metastatic or inoperable neuroendocrine tumours (NETs) is a systemic therapy which targets somatostatin receptors overexpressed by differentiated NETs for endoradiotherapy. This guideline has been compiled by the College of Nuclear Physicians of the Colleges of Medicine of South Africa, with endorsement by the South African Society of Nuclear Medicine and the Association of Nuclear Physicians to guide Nuclear Medicine Physicians in its application during the management of these patients.
Recommendations: Patients with well- to moderately-differentiated NETs should be comprehensively worked-up to determine their suitability for PRRT. Treatment should be administered by a Nuclear Medicine Physician in a licensed, appropriately equipped and fully staffed facility. Patient monitoring is mandatory during and after each therapy cycle to identify and treat therapy-related adverse events. Patients should also be followed-up after completion of therapy cycles for monitoring of long-term toxicities and response assessment.
Conclusion: PRRT is a safe and effective therapy option in patients with differentiated NETs. Its use in appropriate patients is associated with a survival benefit.

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1. Purpose

The aim of this guideline is to assist Nuclear Medicine Physicians in the evaluation, safe administration and follow-up (assessment of response and long-term toxicities) of patients with neuroendocrine tumours (NETs) referred for or considered for peptide receptor radionuclide therapy (PRRT).

This practice guidance was written based on recent publications and opinions of experts routinely using this treatment modality in patient management.

2. Definitions

PRRT: Peptide receptor radionuclide therapy is the administration of a radiopharmaceutical consisting of a beta emitting radionuclide chelated to a peptide. In the treatment of NETs, the peptide is a ligand for the membrane-bound somatostatin receptors. The beta particles emitted by the radionuclide in turn cause DNA damage leading to tumour cell death. The peptide serves as a guidance molecule which homes the beta-emitting radionuclide to the tumour expressing somatostatin receptors. This results in targeted tumour death.

Somatostatin: (SST) is a 14 or 28 amino acid peptide with anti-secretory properties. It occurs naturally mostly in the central nervous system and gastrointestinal tract. The naturally occurring SST has a short half-life due to rapid degradation in vivo. Synthetic analogues of SST have longer biological activity in vivo. Octreotide is an 8-amino-acid derivative of SST.

Somatostatin receptors: (SSTRs) are a group of G protein-coupled membrane-bound receptors that SST and its long-acting analogues interact with to trigger their biologic effects. SSTRs are overexpressed at the cell surface of a large

variety of neuroendocrine tumours. Five main subtypes of SSTRs have been cloned, SSTR 1 to 5. Naturally occurring somatostatin is able to bind to all subtypes of SSTRs but its analogues show major differences in their affinities for the receptor subtypes. Various types of neuroendocrine tumours express the SSTRs in different proportions. SSTR2 is most predominantly expressed by NETs and is therefore commonly targeted for imaging and endoradiotherapy.

Lutetium-177: (Lu-177) is a radiometal that decays by emitting both gamma and beta particles. It has a physical half-life of 6.7 days. Its two gamma particles have energies of 113 keV (6% relative abundance) and 208 keV (11% relative abundance), and are useful for post-therapy imaging and for dosimetry calculation. The maximum and average energies of the beta particles are 0.498 MeV and 0.133 MeV respectively with a corresponding maximum and mean soft-tissue penetration of 1.7 mm and 0.23 mm.

Yttrium-90: (Y-90) is a radiometal that only emits beta particles. It has a physical half-life of 2.7 days. The maximum and mean energies of the beta particle emissions are 2.28 MeV and 0.934 MeV respectively. It has higher tissue penetration compared with Lu-177 with maximum and mean soft-tissue penetration depths of 11 mm and 4 mm respectively.

DOTATATE: DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, is a bifunctional chelator that binds the beta emitting radiometal to the synthetic octreotide. DOTATATE is therefore a derived somatostatin analogue peptide which is an abbreviated form of [DOTA0,Tyr3]-octreotate where Tyr3-octeotide is the synthetic octreotide analogue. DOTATATE has high affinity for the SSTR2 receptor with no significant affinity for other receptor subtypes.[1]

DOTATOC: It is an abbreviation for DOTA0,Tyr3-octreotide. Similar to DOTATATE in that DOTA represents the bifunctional chelator and Tyr3-octrotide is the synthetic octreotide analogue. The octreotide analogue used in DOTATATE has a threonine residue at the C-terminal instead of the corresponding amino alcohol of the octreotide analogue used in DOTATOC. DOTATOC shows the highest affinity for the SSTR2 receptor with a weaker affinity for SSTR3 and SSTR5.[1]

3. Background information

NETs are a heterogeneous group of neoplasms that overexpress SSTRs on their cell surface. They arise from the endocrine cells which are widely dispersed in the body. This explains NETs occurrence in many organs of the body.[2]

NETs may be functional or non-functional. Functional NETs secrete bioactive amines and peptide hormones in accordance with their tissue of origin.[3] Patients with functional NETs are likely to be diagnosed earlier with their disease becoming symptomatic whilst the tumour is still relatively small. NETs are commonly found in the gastroenteropancreatic (GEP) tissues where they may secrete distinct hormones which influences their clinical presentation. The common types of functional NETs include carcinoid, insulinoma, gastrinoma, glucagonoma, VIPoma, and somatostatinoma. Non-functional NETs are commonly slow growing and may only come to clinical detection when they are widely metastatic due to their slow onset of symptom. Other tissues where NETs are commonly found include broncho-pulmonary, genitourinary, breast, and skin.

NETs have previously been described as rare tumours. Their incidence is however rising due to increased awareness amongst physicians and improvements in biochemical testing and diagnostic imaging.[4-6] An increasing number of patients are now diagnosed when the tumours are incidentally detected during diagnostic evaluations for unrelated medical conditions. Patients with genetic predisposition to developing NETs are also now actively sought and followed-up. Many patients with genetic predisposition to NETs are offered prophylactic surgery, for example, total thyroidectomy to prevent the development of medullary thyroid cancer.

The World Health Organization (WHO) has classified NETs into three groups based on the tumour growth rate as demonstrated on histological examination:[7]

- G1 tumours – slow growing well-differentiated tumour (Ki-67 ≤ 2%, mitoses/10 high-power fields < 2)
- G2 tumours – heterogeneous tumours with moderate level of differentiation (Ki-67 > 2% but ≤ 20%, mitoses/10 high-power fields 2-20)
- G3 tumours – poorly differentiated aggressive tumours (Ki-67 > 20%, mitoses/10 high-power fields > 20)

All well-differentiated neoplasm regardless of their metastatic status are called neuroendocrine tumours (NETs). They are sub-classified as either G1 or G2 based on their Ki-67 index. All poorly differentiated neoplasms are termed neuroendocrine carcinomas (NECs) and are graded G3 (Ki-67 > 20%).[8] It is now known that the G3 pancreatic tumour consists of two distinct tumour subtypes: a well-differentiated but highly proliferative group of tumours (Ki-67 > 20%) and a group of poorly differentiated small and large NECs.[9] The 2017 WHO classification of pancreatic neuroendocrine neoplasms has now recognised G3 NETs as a separate entity from NECs.[10]

Disease staging is essential following histological confirmation of the diagnosis. Accurate staging is crucial in determining appropriate therapy. It is important to identify those patients with localised disease in whom disease may be amenable to curative surgical excision. In patients with advanced disease, imaging plays an essential role in determining invasion of tumour into contiguous organs as well as sites of distant metastases. Several organizations including the American Joint Committee on Cancer (AJCC), European Neuroendocrine Tumour Society (ENETS), WHO and the Union for International Cancer Control (UICC) have individually or jointly proposed staging systems for some of the most common types of NETs.[7,11,12] Tumour grading and disease stage have prognostic value in patients with NETs.[7,13-15]

Conventional imaging with contrast-enhanced computed tomography (ceCT) and magnetic resonance imaging (MRI) are the primary investigations obtained in staging and re-

staging of disease. Three-phase examination of the liver on a ceCT is essential for adequate evaluation of liver involvement. MRI is useful for the evaluation of liver, pancreas, bone marrow and brain involvement. Ultrasound is a useful modality to provide guidance for image-guided biopsy.[16]

Functional imaging with Gallium-68 (Ga-68) DOTA-peptide (including Ga-68 DOTATATE, Ga-68 DOTATOC and Ga-68 DOTANOC) has demonstrated the highest sensitivity and specificity in the evaluation of most types of NETs with an overall sensitivity of > 90% and specificity ranging between 92 and 98%.[1,17] Positron emission tomography (PET) imaging with Ga-68 DOTA-peptide has superiority over single photon emission tomography (SPECT) imaging with Indium-111 or Tecnetium-99m octreotide.[18,19]

Studies have demonstrated the strengths of Ga-68 DOTA-peptide over conventional anatomic imaging with computed tomography (CT) or MRI in the evaluation of patients with NETs.[19-21] It is better than CT at detecting bone metastases due to neuroendocrine tumour.[22] In a study, Ga-68 DOTATATE PET/CT was found to outperform standalone ceCT in the detection of neuroendocrine tumour metastases in the bones and lymph nodes. Both modalities had similar sensitivity in the detection of pulmonary metastases but Ga-68 DOTATATE had a significantly higher specificity.[23] The excellent soft tissue resolution of MRI combined with the high sensitivity of Ga-68 DOTA-peptide may make combined functional and morphologic imaging with Ga-68 DOTA-peptide PET/MRI a useful modality for imaging especially for lesion detection in the pancreas and liver.[24]

4. Treatment options for neuroendocrine tumours

Several therapy options are available for the treatment of neuroendocrine neoplasms depending on disease stage, tumour differentiation, genetic alterations in the tumour, among others. It is therefore prudent that therapy decision be undertaken in a multidisciplinary team including Endocrine Surgeons, Oncologists and Nuclear Physicians.

Surgical resection with curative intent is the treatment of choice in patients with localised disease and in patients with liver/lymph node metastases.[25] Surgical resection of the primary tumour in patients with metastatic NETs may reduce the incidence of complications such as intestinal obstruction and may have survival benefit.[26] Surgical de-bulking of tumours may be undertaken in patients with large tumours.

In patients with liver metastases which are not resectable, liver-directed therapies such as trans-arterial chemoembolization, trans-arterial embolization (TAE), radiofrequency ablation, and selective internal radiation therapy (SIRT) may be employed to down-stage liver metastases so that they can be resected. If employed earlier in the disease course, TAE has been shown to be associated with better tumour response and overall survival. These treatments may also be offered for symptom control in functional NETs.[27]

In patients with advanced disease that is not amenable to curative surgical resection, treatment is directed at controlling excess hormone secretion by the tumour cells and inhibition of the tumour. The long-acting somatostatin analogues, octreotide and lanreotide are currently considered for first line treatment. The growth inhibitory effect of the somatostatin analogues is the basis for their use even in non-functional NETs expressing SSTR2 with rapid tumour growth.[28]

The CLARINET study is a phase III trial that randomised patients with grade 1 or 2 gastroenteropancreatic NETs to either receive an extended-release form of lanreotide (n=101) or placebo (n=103). The primary end point was progression-free survival (PFS). Lanreotide was found to be associated with a significant PFS compared with placebo with a PFS at 24 months of 65.1% (95% CI, 54.0 to 74.1) for the lanreotide group compared with 33.0% (95% CI, 23.0 to 43.3) for the placebo group.[29] The PROMID trial randomly assigned treatment-naïve patients with mid-gut well-differentiated metastatic NETs to either placebo or 30 mg intramuscular injection of octreotide LAR.[30] Median time to tumour progression was 14.3 months in the octreotide group versus 6 months in the placebo group (hazard ratio=0.34; 95% CI, 0.20 to 0.59, p=0.000072). No difference in response rates was seen in patients with functional NETs compared to patients with non-functional NETs.

NETTER-1 is a phase III trial that randomly assigned patients with well-differentiated metastatic midgut neuroendocrine tumours to either receive Lu-177 DOTATATE every 8 weeks with best supportive care including 30 mg intramuscular injection of long-acting repeatable (LuTATE group, n=116) or 60 mg intramuscular injection of LAR octreotide every 4 weeks (control group, n=113).[31] The estimated PFS at 20 months was 65.2% (95% CI, 50.0 to 76.8) in the LuTATE group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the LuTATE group compared with 3% in the control group ($p < 0.001$). Grade 3 or 4 neutropenia and thrombocytopenia were seen in 1% and 2% respectively of patients in the LuTATE group compared with none in the control group. No evidence of renal toxicity was reported in the study.

The 2010 WHO tumour grade is an important factor to be considered in deciding on appropriate tumour-targeted therapy. In patients with poorly differentiated, rapidly proliferating G3 NEC, chemotherapy is indicated. Chemotherapy may also be indicated in patients with extra-pancreatic NETs (e.g. bronchial, thymus, stomach, colon, rectum) with Ki-67 in the upper G2 range. Other situations in which chemotherapy may be considered include rapid tumour progression in less than 6 to 12 months, as neoadjuvant therapy to downstage tumour to allow for surgical resection, following failure of other therapies, large tumour bulk, and in the event of a negative somatostatin-based functional imaging.[25] Cisplatin or carboplatin with etoposide are preferred for NECs. Chemotherapy with agents such as 5-FU, capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide in different combinations may be used in G1 or G2 tumours when indicated.[32-34] Chemotherapy has limited utility in patients with slow-growing well-differentiated tumour.

The utility of molecular target agents is being evaluated in several clinical trials. These agents target different pathways in tumourigenesis. Everolimus is a mTOR inhibitor associated with improved PFS. The RADIANT-3 study reported the overall survival (OS) in patients with advanced, progressive, low- to intermediate-grade pancreatic NETs randomly assigned to everolimus or placebo.[35] Everolimus was associated with an OS of 44.0 months compared with OS of 37.7 months in the placebo group (survival benefit of 6.3 months). This survival benefit was however not significant (p=0.30). In the updated progression-free survival and overall survival from the double-blind, placebo-controlled trial that randomised patients with advanced, well-differentiated, progressive pancreatic neuroendocrine tumour to either receive 37.5 mg/day sunitinib (n=86) or placebo (n=85), median progression-free survival was 12.6 months (95% CI: 11.1-20.6) for sunitinib versus 5.8 months for placebo group (95%CI: 3.8-7.2) (hazard ratio, 0.32; 95% CI 0.18-0.55; p=0.000015). There was however no significant difference in the overall survival between the two groups.[36]

5. Indications and contraindications

5.1 Indications

PRRT with Lu-177 DOTATATE or Y-90 DOTATOC is indicated in patients with SSTR2 positive metastatic or inoperable NETs.[31,37-40] The ideal patient must have a well- to moderately-differentiated tumour (2010 WHO G1 and G2). Published data are most robust for use of PRRT in patients with SSTR-expressing gastroenteropancreatic and bronchial NETs. Other NETs such as pheochromocytoma/paraganglioma, neuroblastoma and medullary thyroid carcinoma are possible indications for PRRT.[41-43] In view of the highly heterogeneous nature of G3 tumours,[44,45] PRRT may be considered in patients with G3 pancreatic NETs whose lesions demonstrate tracer avidity on Ga-68 DOTA-peptide imaging.[46,47]

The decision to consider patients with G3 NETs for PRRT as well as the need for addition of radio-sensitising chemotherapy to therapy should be made in a multidisciplinary setting.

The ideal candidate for PRRT should fulfil these criteria:

- Histologically confirmed well-differentiated NET- or moderately-differentiated NETs, G1 or G2
- Advanced disease that is not amenable to curative surgery
- Progressive disease
- SSTR2 positive disease demonstrated on functional imaging (intensity of tracer uptake in lesions greater than the physiologic uptake within normal liver tissue) which is concordant with morphological imaging. If there is discordance, an FDG PET/CT should be done to assess concordance with SSTR2 positive disease
- Karnofsky performance status above 60% or ECOG performance status < 2.

5.2 Contraindications

Absolute

- Pregnancy
- Severe acute intercurrent illness

Relative

- Poor bone marrow reserve: white blood cell count < 2,000/µL, platelet count < 75,000/ µL, haemoglobin concentration < 8 g/dL.
- Severely impaired renal function: serum creatinine > 150 µmol/L. Y-90 and Lu-177 used in PRRT undergo tubular reabsorption following their filtration at the glomerulus. Patients with obstruction in their renal outflow tract have a high radiation dose delivered to their kidneys. Such patients are recommended to undergo a procedure to relieve outflow obstruction before they are submitted to PRRT.
- Compromised liver function: total bilirubin level > 3 times upper limit of normal, serum albumin < 3.0 g/dL.

6. Procedure

6.1 Facility and personnel

PRRT is a radionuclide therapy and must be used in compliance with the national regulations. It must be administered in an appropriately equipped facility licensed by the radiation control unit of the Department of Health (DoH) as suitable for the safe administration of radionuclide therapies. The facility must be staffed with personnel who are well trained in the safe use of unsealed radiation sources including waste management and handling of accidental contamination of persons and the site. PRRT must be administered by a Nuclear Medicine Physician with supporting staff (medical physicist and nursing).

6.2 Preparation for therapy

Somatostatin analogues withdrawal:

Withdrawal of somatostatin analogues (SAs) prior to PRRT is still a subject of intense debate. No consensus has been reached as to whether its use has any significant impact on uptake of Lutetium 177 DOTATATE by the tumour. We recommend withdrawal of SAs prior to PRRT. Short acting SAs should be withdrawn for 24 hours and long acting SAs should be withdrawn for 1 month.

Once considered for PRRT, the following must be done within two weeks of the proposed date of therapy to confirm eligibility:

- Review patient history and make a comprehensive documentation of it
- Full blood count
- Renal function test – serum creatinine and creatinine clearance to estimate glomerular filtration rate. Cr-51 EDTA or Tc-99m DTPA glomerular filtration rate (GFR) determination may be preferred in high-risk patients: diabetes, hypertension, previous renal insult, pretreatment with chemotherapy, solitary kidney, and children.
- Radionuclide dynamic renal scintigraphy to evaluate for outflow obstruction
- Liver function tests including international normalised ratio (INR) and prothrombin time
- Serum chromogranin A and other relevant tumour-specific biomarkers for biochemical response assessment
- Perform a comprehensive physical examination including performance status determination.

6.3 Therapy administration

Informed consent must be obtained from the patient prior to therapy administration.

Renal protection:

The kidneys are the target organs during PRRT.

Renal protection is indicated to prevent the reabsorption of the therapy agent by the tubular cells responsible for renal toxicity. This is done by infusion of the positively charged amino acids L- lycine and/or L-arginine which compete with Lu-177 DOTATATE or Y-90 DOTATOC for tubular reabsorption, reducing radiation dose to the kidneys.[48] Different protocols for renal protection have been described.[49] Aminostetil® N-Hepa 8% is an amino acid solution available for intravenous infusion in South Africa. We recommend intravenous administration of 1.5 to 2 litres of this amino acid solution given over 4 hours using an infusion pump. Amino acid infusion should be started 30 to 60 minutes before administration of the therapy agent.

Premedication:

Premedication is given prior to commencement of amino acid infusion to mitigate against the side effects of its administration. These medications are:

- 4 mg intravenous Dexamethasone
- 8 mg intravenous Ondansetron

Lu-177 DOTATATE:

Lu-177 DOTATATE is available in South Africa. It is delivered to the therapy centre in a ready-to-use form after passing all quality control tests and must be administered to the patient on the same day. It is administered as follows:

- Activity – 150 to 200mCi (5.55 to 7.4 GBq) in 50 to 100 mLs of normal saline infused over 30 minutes. Lower activity of about 100mCi (3.5GBq) may be considered in children.
- Numbers of cycles – 4 to 6
- Treatment interval – 8 to 12 weeks.

Post-therapy images:

Post-therapy images are obtained from imaging the 208 KeV gamma photons of Lu-177. Whole-body planar images obtained at 4-time-points (for example, at 1, 4, 24 and 48 hours post-therapy) to confirm uptake of therapy agents in the tumour and for dosimetry assessment. Further delayed imaging may be acquired for dosimetry assessment. Additional single photon emission computed tomography and computed tomography (SPECT/CT) imaging of the abdomen may be performed at 24 hours post-therapy.

Treatment can be performed on an in- or outpatient basis. This decision is made by the attending Nuclear Physician and is usually based on the patient's medical condition.

The South African regulations require that patients treated with radionuclide therapy must have their exposure rate below 25 µSv/hr at a distance of 1 metre from the patient before discharged home.

Special precautions:

The treating Nuclear Physician must ensure that the patient for PRRT does not have any contraindication to the therapy agent or other additional agents routinely administered during therapy. For example, dexamethasone should be omitted in patients with pheochromocytoma/paraganglioma. In paediatric patients, amino acid should be infused at a slower rate.

7. Side effects

7.1 Acute

There are side effects related to amino acid infusion and the therapy agent. Infusion of concentrated amino acid solution may lead to nausea, headache, abdominal discomfort and vomiting due to metabolic acidosis.[31,37] Rapid infusion of the amino acid solution may cause a patient with borderline cardiac function to develop cardiac insufficiency. In this category of patients, a lower volume of amino acid solution should be administered.[49] Electrolyte derangements such as hyperkalaemia and hypernatremia may also complicate amino acid infusion.

Therapy agent administration may worsen the clinical symptoms related to the syndromes present in patients with functional NETs. The specific nature of these side effects will depend on the type of NETs. Therefore, look out for adrenergic crisis in patients with pheochromocytoma/paraganglioma, carcinoid crisis in patients with carcinoid tumour, and tumour lysis syndrome in patients with large tumours. Patient must therefore be monitored continuously throughout their hospital stay while being observed for any adverse effect.

7.2 Delayed

Hematotoxicity is the most common delayed side effect following PRRT.[31,37] This may occur 4 to 8 weeks after treatment in the form of anaemia, thrombocytopenia or leucopenia.[37] Treatment related cancers in the form of myelodysplastic syndrome and acute leukaemia have been reported in 1–4 % of patients treated with PRRT.[31,37,50-53] The incidence of treatment-related hematologic malignancies is related to the duration of follow-up. The mean latency time for the development of myelodysplastic syndrome or acute leukaemia in patients treated with PRRT is > 40 months.[50,52] Previous use of myelotoxic chemotherapy and radiotherapy to red marrow are strong predictors of hematotoxicity following PRRT. Other factors predisposing to hematological malignancies are tumour invasion of the bone marrow and hematological toxicity grades 3/4 during the course of PRRT.[50,52]

Serious renal toxicity is rare. Factors predisposing to deterioration in renal function following PRRT include renal outflow obstruction, and pre-existing hypertension and diabetes. In the NETTER 1 trial, no patient with grade 3 or 4 renal toxicity was reported.[31] In a separate study, 2 patients out of 504 treated with Lu-177 DOTATATE for NETs had renal insufficiency, one of whom had a pre-existing renal impairment.[37]

Liver toxicity may be seen in patients with extensive liver metastases resulting in irradiation of the limited functioning liver tissue.[37] Other potential long-term side effects include mild hair loss, asthenia, and decreased appetite.

8. Follow-up

8.1 Between-treatment

During the treatment period, certain biochemical investigations should be obtained to detect side effects and determine patients' eligibility for subsequent treatment cycles. The following tests should be done two weeks before each scheduled treatment cycle:

- Full blood count
- Serum electrolyte, urea and creatinine including estimated GFR determination
- Liver function tests including prothrombin time
- Chromogranin A and any other relevant tumour specific biomarkers
- Dynamic renal scintigraphy should be repeated before the third and fifth treatment cycles
- Functional and radiological imaging may be considered if clinically indicated.

8.2 Post-therapy

After completion of treatment cycles, patients are usually referred back to their referring clinicians. It should be suggested in the discharge summary that patients should have repeat full blood count, liver function test, serum creatinine, eGFR and biomarkers done every 12–16 weeks. Morphologic imaging with ceCT and/MRI should be done 3–6 months after completion of PRRT to document objective response to therapy. Ga-68 DOTA-peptide PET/CT imaging provides an opportunity for the evaluation of the functional status of the disease post-therapy. This functional imaging may be done 6–12 months after the last cycle of PRRT. Combined morphologic and functional imaging may be complementary in post-PRRT assessment. Subsequently, patients should have Ga-68 DOTA-peptide PET/CT annually (or sooner if clinically indicated) for follow-up.

When there is a discordance between morphologic and metabolic imaging which may suggest tumour dedifferentiation resulting in loss of avidity of tumour for Ga-68 DOTA-peptide, F-18 FDG PET/CT should be done. Intense avidity of F-18 FDG in tumour, incongruent with finding on Ga-68 DOTA-peptide, supports tumour dedifferentiation.[53,54] This may be confirmed by re-biopsy of lesion. Chemotherapy should be considered in the retreatment of patients whose lesions no longer express the SSTRs.

9. Salvage therapy for recurrent disease

Salvage therapy with PRRT may be considered for retreatment with PRRT provided there was no severe toxicity to the previous treatment.[55,56] This decision must be taken in a multidisciplinary setting. Patients being considered for retreatment should be evaluated afresh for suitability for PRRT as they were initially.

10. Outcome and Goals of Therapy

PRRT in progressive SSTR positive NETs leads to complete remission in a minority of patients. The majority of patients (70–90%), however, have partial/minor response or stable disease. A minority of patients (4–10%) may experience progressive disease despite treatment.[57-59] Symptomatic response is achieved in more than 90% of patients with functional NETs.[60] Response achieved with PRRT is durable with median progression-free survival of 26–33 months and median overall of 55–61 months.[57-59] Several factors predict outcome of treatment. Factors predictive of good therapy outcome and long-term survival include low Ki-67 index, Karnofsky performance index score $\leq$ 70%, liver tumour burden $\geq$ 25% of total hepatic volume, baseline serum neuron-specific enolase < 15 ng/mL, and NETs of small bowel origin.[59,60]

The goal of treatment with PRRT is therefore palliative in the form of symptomatic control in patients with functional NETs, tumour growth control, and improvement in quality of life.[61] Sufficient down-staging of tumour may be achieved after PRRT allowing for tumour resection.

11. Disclaimer

This practice guidance document has been written by the College of Nuclear Physicians (CNP) of South Africa and endorsed by the South African Society of Nuclear Medicine (SASNM) and the Association of Nuclear Physicians (ANP) to assist Nuclear Physicians in providing appropriate care for patients and as an educational tool to promote cost-effective use of PRRN in clinical practice and in research. These guidelines should be used as a guidance document for clinicians and not a set of rules to be rigidly applied to all patients. The judgement on the course of patient management should be made by the physician based on circumstances presented. In view of this, a course of action that differs from what is stated in this document is not necessarily below the standard of care. The CNP and the SASNM caution against the use of this guidance document as a legal standard of care or its use in litigation to challenge the clinical decisions of a practitioner.

This document has been compiled based on recent published evidence in the literature on the use of PRRT in the management of differentiated NETs as well as the experience of leading practitioners in the field. Evidence advancing the practice of Nuclear Medicine emerges at a rapid rate. The date of publication of this document should be considered in the determination of its applicability at all times.

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