Practical Guidance on Peptide Receptor Radionuclide Therapy (PRRNT) for Neuroendocrine Tumours
FOREWORD

Peptide Receptor Radionuclide Therapy (PRRNT) using Yttrium-90 DOTATOC was first administered in the year 1996 to a patient in Basel, Switzerland. The objective was to stabilize the progression of the disease in a 40-year-old patient with gastroenteropancreatic neuroendocrine tumour (NET) proven refractory to conventional chemotherapy. The excellent subjective and objective response after several treatment cycles prompted exhaustive pre-clinical and clinical research to explore the therapeutic potential of PRRNT for the treatment of NET tumours. Since then PRRNT using Y-90 or Lu-177 DOTATOC has acquired wide acceptance and spread in many medical centres in Europe and more recently in other major centres around the globe.

This document is part of a larger endeavour of the Department of Nuclear Sciences and Applications to address the rising need of Member States to introduce therapeutic applications of unsealed radioisotopes in clinical routine practice.

NET is a unique sub-class of cancer in which a good percentage of affected patients may experience disease control following several cycles of PRRNT while improving symptoms and quality of life in the majority of cases. This book is a practical reference for specialists in Clinical Oncology and in Nuclear Medicine embarking on deploying and executing a comprehensive programme for treating patients with neuroendocrine tumours.

Practical Guidance on Peptide Receptor Radionuclide Therapy for Neuroendocrine Tumours is a milestone providing comprehensive multi-disciplinary guidance to enhance the effective, safe and standardized implementation of best practice for treating patients with NET and gastroenteropancreatic (GEP) cancer with due regard to the recent international classifications of neuroendocrine tumours. This book embarks on providing comprehensive protocols for employing either Yttrium-90 or Lutetium-177 tagged somatostatin receptor-targeting peptides and clinically assessed protocols for renal protection. It is a comprehensive compilation of clinically based evidence with input of experienced and renowned medical professionals in this field. The book covers clinical presentations, eligibility criteria, and means of assessing effectiveness of therapy utilizing molecular and morphological medical imaging techniques.

The decision on whether or not to prescribe PRRNT is to be made by the treating medical physicians in consideration of histological reports, anatomical and functional imaging, previous therapeutic regimens, cumulative irradiation dose to critical organs and existing risk factor in the susceptible patient. In selected patients, adopting treatment strategy different from that set forth in this book, undertaken by the conscientious physician, may be appropriate, tailored to the condition of the patient or governed by other circumstances, e.g. the availability of the radiopharmaceutical, or advances in knowledge subsequent to the publication of this guidance.

We are indebted to the contributors and reviewers, whose names are provided in an alphabetical order at the end of this document, for sharing their invaluable knowledge, time and effort to achieve a consensus on the guidance provided herein. The scientific secretary responsible for this book has been Mr. J. Zaknun of the Nuclear Medicine Section, Division of Human Health.
EDITORIAL NOTE

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1. INTRODUCTION

1.1. Background

Peptide Receptor Radionuclide Therapy (PRRNT) is an established treatment of neuroendocrine tumours (NET) in Europe and is emerging in other areas around the world. Neuroendocrine tumours are rare, but their incidence is increasing worldwide. Because these tumours can arise in any tissue with endocrine cells and symptoms of disease are vague and variable, the identification of the primary tumour is difficult. Molecular imaging of the whole body with receptor targeted radionuclides ($^{111}$Indium, $^{99m}$Technetium and $^{68}$Gallium) has greatly enhanced the diagnosis of both primary and metastatic lesions as well as providing prediction of response to PRRNT. Image-guided PRRNT is an effective therapy in NET which are unresponsive to conventional chemotherapy.

1.2. Objective

The purpose of this guideline is to enable multidisciplinary teams in IAEA Member States to implement this novel therapy in a safe and effective manner for the treatment of neuroendocrine tumours. It provides theoretical and practical knowledge on the biology, indications, diagnosis, and current therapeutic options for the treatment of NETs. An additional goal is to provide a framework for the integration of PRRNT into current practice of conventional cancer treatments modalities including surgery, chemotherapy, external beam radiotherapy, biological, locoregional, and molecular targeted treatment approaches.

The ultimate objective is to enable cancer care facilities in Member States to incorporate diagnostic imaging and PRRNT into their battery of treatment options for patients with neuroendocrine tumours. This book, in addition, aims at harmonizing and achieving a high level of standardization of the treatment protocols for the delivery of this unique therapy.

1.3. Scope

This book provides guidance for diagnosis, imaging and delivering PRRNT for differentiated NETs and gastroenteropancreatic NETs. Diagnosis is based on WHO guidelines for grading and staging with emphasis on the importance of correct diagnosis as related to PRRNT. Methodology and imaging guidelines are provided for anatomical and functional imaging of neuroendocrine tumours including the use of PET, CT, MRI and ultrasonography. The rationale and protocols for safe and effective administration of PRRNT are provided in sufficient detail to allow the implementation of this treatment in advanced nuclear medicine facilities of any Member State.

1.4. Structure

The chapters are divided into clinical presentation and diagnosis of neuroendocrine tumours in adults and children, the appropriate use of both anatomical and molecular imaging, wholistic care of patients with neuroendocrine tumours, and finally the appropriate indications for the use of PRRNT alone or in combination with other available treatment options of NET. The assessment of response to treatment is discussed within each relevant chapter. Finally, a short chapter provides an overview on the principles of dosimetry followed by an annex with a roadmap summarizing recent relevant publications to assist in performing dosimetric calculations of radiation absorbed doses to tumour and kidneys. Annex 2 contains structured clinical history form, and annex 4 comprises details on formulating a PRRNT-specific
“patient’s informed consent form” followed by exhaustive sample covering relevant information prior and following the delivery of PRRNT to NET patients.
2. NEUROENDOCRINE TUMOURS AND PRRNT

2.1. Rationale

(PRRT is the systemic or locoregional administration of a radiopharmaceutical composed of an β-emitting radionuclide chelated to a peptide for the purpose of delivering cytotoxic radiation to a tumour. The peptides used are designed to target cellular proteins, usually cell-surface receptors, such as the somatostatin receptor subtype 2 (sstr2). This subclass of receptors is over-expressed in a tumour-specific pattern, thus providing specificity to the radiation delivery. PRRT is a molecularly targeted radiation therapy in contrast to external beam radiotherapy. The delivery of PRRT is performed over multiple cycles, usually administered at 8 - 12 weeks apart.

PRRT is the result of synergistic collaborations between peptide chemists, endocrinologists, gastro-enterologists, and nuclear medicine physicians. Together they designed stable, highly specific peptide analogs of endogenous peptide ligands and developed chelators to bind the radionuclides with near irreversibility. Initial nuclear medicine imaging studies provided elegant pictures that precisely demonstrated the specificity of peptide ligands for receptors in vivo, providing vivid illustration of how higher energy, cytotoxic radionuclides may be targeted to malignant tumours. The application of peptide-receptor pharmacology to functional imaging and now to molecularly targeted radiotherapy is a fascinating example of translational medicine.

Neuroendocrine tumours have proven to be ideal neoplasms in which to exploit PRRT, as the majority of these slow-growing malignancies over-express somatostatin receptors. Furthermore, the endogenous ligand, somatostatin, is a small, cyclic peptide which lends itself to both chemical stabilization through substitution of D-amino acids and attachment of a chelating moiety to bind radionuclides, while retaining high affinity for the target receptor [1]. Initial attempts at functional nuclear medicine imaging of NETs provided surprisingly clear demonstrations of the specificity and sensitivity of $^{111}$In-DTPA-Octreotide for the somatostatin receptor in gastroenteropancreatic tumours [2] and paved the way for PRRT using $^{90}$Y-DOTA-tyr3-Octreotide and $^{177}$Lu-DOTA-Octreotate [3, 4]. These two radiopharmaceuticals remain the primary agents used for PRRT in current practice.

The purpose of this guideline is to enable multi-disciplinary teams in IAEA Member States to implement this novel therapy in a safe and effective manner for treatment of neuroendocrine tumours. An additional goal is to provide a framework for integration of PRRT into current practice with conventional cancer treatments including surgery, biologics, chemotherapy, locoregional liver treatments, external beam radiotherapy, and molecularly targeted therapies.

2.2. Epidemiology

Neuroendocrine tumours arising from the diffuse endocrine system can occur in any organ of the body. The most common sites are ileum, pancreas, and lung, with NET in thymus, breast, stomach, colon, ovary, and cervix being less common.

The incidence of neuroendocrine tumours has been rising over the past 30 years as documented by Yao et al. [5] who analyzed the SEER database in the United States, Hauso et al., who compared U.S. and Norway [6], and Hegde in the Asia-Pacific region [7]. This increase in NET incidence is most pronounced in midgut and pancreatic NET [8]. Overall, the incidence rate rose from 10.9 to 52.4/million in the United States from 1973 to 2004 [5].
From these combined registries, the incidence is now recognized as 38 per million persons per year referenced to 2004 in the USA. Incidence in multiple countries is shown in Table 2.1; please note that incidence appears lower in most early studies.

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (millions)</th>
<th>Estimated incidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>22</td>
<td>not available</td>
<td>[10]</td>
</tr>
<tr>
<td>Brazil</td>
<td>192</td>
<td>not available</td>
<td>[15]</td>
</tr>
<tr>
<td>Denmark &amp; Norway</td>
<td>6 + 5</td>
<td>11.0 (carcinoid only)</td>
<td>[12]</td>
</tr>
<tr>
<td>Europe</td>
<td>830</td>
<td>survival data only</td>
<td>[19]</td>
</tr>
<tr>
<td>Germany</td>
<td>82</td>
<td>not available</td>
<td>[16]</td>
</tr>
<tr>
<td>India</td>
<td>1178</td>
<td>not available</td>
<td>[7]</td>
</tr>
<tr>
<td>Italy</td>
<td>60</td>
<td>6.5 (GI carcinoid only)</td>
<td>[13]</td>
</tr>
<tr>
<td>Japan</td>
<td>127</td>
<td>31.1</td>
<td>[18]</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16</td>
<td>18.5</td>
<td>[9]</td>
</tr>
<tr>
<td>Sweden</td>
<td>9</td>
<td>24.3 (carcinoid only)</td>
<td>[11]</td>
</tr>
<tr>
<td>Switzerland</td>
<td>8</td>
<td>22.5 (carcinoid only)</td>
<td>[17]</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>62</td>
<td>8.2 (carcinoid only)</td>
<td>[14]</td>
</tr>
<tr>
<td>United States</td>
<td>309</td>
<td>38.5</td>
<td>[5]</td>
</tr>
</tbody>
</table>

Recognizing the slower growth of most neuroendocrine tumours with associated longer survival of these patients, the prevalence of neuroendocrine tumours is significant. Survival data are not available for most of the above studies; however, Yao estimated the U.S. prevalence of NET at 103,000 as of January 1, 2004 [5] and Ito estimated prevalence of NET in Japan at 39,500 [18]. Many, if not most, patients with NETs can lead high-quality lives while being treated. Thus, a new treatment such as PRRNT, with few side effects, is highly desirable in that it allows these patients to continue as productive members of society [20].

2.3. Introduction to classification systems

Neuroendocrine tumours arise from the diffuse endocrine cell system. The term “carcinoid” was first introduced by the German pathologist Oberndorfer in 1907 for serotonin producing tumours in the small intestine with benign behaviour [21]. Williams and Sandler first attempted a systematic classification of gastroenteropancreatic NET in 1963 [22]. They subdivided NETs according to their origin in the embryonal gut and named them foregut, midgut, and hindgut neuroendocrine tumours. Although this classification is of limited prognostic significance, it is still in use for the reason of anatomic characterization of primary tumour localization in patients with NET.
In 1980 the World Health Organization (WHO) suggested a classification system in which carcinoid tumours (including NETs derived from gastrin-producing G-cells) were separated from pancreatic tumours and a few other endocrine tumours, such as Merkel cell carcinoma, paragangliomas, and others. This classification also was unsatisfactory with respect to both adequate histologic classification and prognostically relevant clinicopathologic categorization.

In 1980 Capella et al. [23] attempted a new clinicopathologic classification system which considered macroscopic features (e.g. size and metastasis), histopathologic features (e.g. cellular differentiation, neuroinvasion, angioinvasion, and lymphangioinvasion, proliferation index) and clinical features (e.g. the presence of hormone hypersecretion syndromes) as well as hereditary background. This classification generally separated benign neuroendocrine tumours from those with uncertain behavior, low-grade malignant neuroendocrine carcinomas, and high-grade malignant neuroendocrine carcinomas.

In 2000 the WHO published a revised classification system for the histologic typing of endocrine tumours [24]. This classification distinguishes well differentiated endocrine tumours (WDET), well differentiated endocrine carcinomas (WDEC), and poorly differentiated endocrine carcinomas (PDEC) and includes the location of the primary tumour as a classification criterion.

<table>
<thead>
<tr>
<th>TABLE 2.2. COMPARISON OF ORIGINAL AND UPDATED WHO GRADING SYSTEM FOR NEUROENDOCRINE TUMOURS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO 2000 [24]</strong></td>
</tr>
<tr>
<td>WDET: Well differentiated (neuro)Endocrine Tumour</td>
</tr>
<tr>
<td>WDEC: Well Differentiated (neuro)Endocrine Carcinoma</td>
</tr>
<tr>
<td>PDEC: Poorly Differentiated (neuro)Endocrine Carcinoma</td>
</tr>
<tr>
<td>- Large cell</td>
</tr>
<tr>
<td>- Small cell</td>
</tr>
<tr>
<td>Mixed Exocrine Endocrine Carcinoma</td>
</tr>
<tr>
<td>Tumour-like lesions</td>
</tr>
</tbody>
</table>

In 2006 the European Neuroendocrine Tumour Society (ENETS) recommended a standardized classification system for gastroenteropancreatic (GEP) NETs according to the TNM system. This classification can serve to guide clinical management and to harmonize and standardize patients’ selection in the framework of appropriate design of clinical trials.
This is analogous to the TNM classification systems used for other solid tumours and was the result of a consensus conference of international experts held by ENETS. This TNM classification was incorporated into the latest WHO classification for digestive system tumours in 2010 [27].

TABLE 2.3. GRADING OF NEUROENDOCRINE TUMOURS ACCORDING TO ENETS [25, 26]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitosis (10HPF)(^a)</th>
<th>Ki-67 Index (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt; 2</td>
<td>&lt;= 2</td>
</tr>
<tr>
<td>G2</td>
<td>2 - 20</td>
<td>3 – 20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

\(^a\) 10 HPF: high power field = 2mm\(^2\), at least 40 High power fields (40x),

\(^b\) MIB-1 Antibody; % of positively stained of 2000 tumour cells

This most recent classification system provides guidelines for both staging and grading, the latter of which characterizes the proliferative potential of neuroendocrine tumour cells using either the mitotic count or the Ki-67 labelling index [28].

At this point the WHO classification is historically the most evolved and enduring; it has been adapted by European countries and by the ENETS community. It is also the most widely applied. It is important to emphasize that currently both the WHO and the TNM classification are used in parallel to provide independent prognostic information and for classifying these tumours. The latest version of the TNM classification of NETs can be retrieved from the homepage of the Union Internationale Contre le Cancer (UICC; www.uicc.org).

For NET of the thorax including bronchopulmonary and thymus there is a separate WHO classification subdivided into four groups: typical carcinoid, atypical carcinoid, large cell NE carcinoma, small cell NE carcinoma [29, 30]. For details please see Table 2.4.


<table>
<thead>
<tr>
<th>Type</th>
<th>Differentiation Grade</th>
<th>Mitosis per 2mm(^2) (10HPF)</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid</td>
<td>well differentiated</td>
<td>&lt; 2</td>
<td>no necrosis</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>well differentiated</td>
<td>2-10</td>
<td>with/ without necrosis</td>
</tr>
<tr>
<td>Large cell neuroendocrine</td>
<td>poorly differentiated</td>
<td>11; median: 20</td>
<td>with necrosis; large cells</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
<td>with necrosis; small cells</td>
</tr>
<tr>
<td>Small cell neuroendocrine</td>
<td>poorly differentiated</td>
<td>11; median: 80</td>
<td></td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the USA a modified classification system has been adapted and the NANETS (North American Neuroendocrine Tumour Society) consensus recommendation was published in 2010 [31].

It is important, for therapeutic decision making, to receive a complete pathological report including synaptophysin and chromogranin A (Cg-A) staining in order to confirm the neuroendocrine nature and to determine tumour grade utilizing counting percent mitoses or Ki67 staining in at least 2000 cells. It is worth noting that Cg-A is expressed in high abundance in well differentiated NET, but is less expressed in poorly differentiated NET, while synaptophysin is more consistently expressed in poorly differentiated NET. The grading is especially critical to assure appropriate therapeutic management, as in high grade NET ($\geq$ G3 with Ki-67 $>$ 20%) chemotherapy becomes the primary option for therapy.

Though not routine in most centers, somatostatine receptor type 2 (sstr2) expression by immunohistochemistry can be helpful in determining differentiation status, as it is expressed in 70% up to 100% of highly differentiated NETs. Clinically this is best defined by functional scintigraphy (OctreoScan® / $^{68}$Ga-PET-CT scan). Both scintigraphy and immunohistochemistry are of limited value in poorly differentiated NET ($\geq$ G3 wherein OctreoScan® has only 20-30 % sensitivity).

Thus, the minimum histopathological data set is described as the process that is recommended for the pathologist to provide the clinician with information sufficient to make the best decision possible for the patient’s further care [32].

2.4. Clinical presentation

2.4.1. Introduction

The clinical presentation may vary depending on the site of tumour origin. About 72% of neuroendocrine tumours arise in gastrointestinal structures, further 25% are broncho-pulmonary in origin, and less than 5% arise at other sites (e.g. thymus, breast and genital-urinary system).

NETs of the GEP system are comprised of cells capable of amine precursor uptake and decarboxylation cells previously termed APUDomas. Characteristics of NET are episodic hormone secretion/release and indolent slow growth; thus, they may be silent for years.

Although all these tumours are expressing one or more amines and/or polypeptides, only 40-50% are functionally active resulting in specific clinical symptoms or syndromes. Although less than 10% of midgut tumours are associated with carcinoid syndrome, it is the most frequently observed syndrome among all NETs. It is understood that metastases exist in the presence of the carcinoid syndrome, as most are associated with metastases to the liver.

Those tumours which are secreting physiologically important amounts of hormones or amines are termed according to the predominant secretory substance, e.g. gastrin- Zollinger Ellison syndrome/gastrinoma (Table 2.5). The most frequent syndromes are the carcinoid syndrome (serotonin-producing tumours predominantly of the gastro-intestinal system), followed by insulinoma and gastrinoma (both predominantly from the pancreas), and gastrinoma associated with the hereditary syndrome Multiple Endocrine Neoplasia Syndrome Type 1 (MEN-1), primarily duodenal in origin.
### TABLE 2.5. NEUROENDOCRINE TUMOURS: CLINICAL SYNDROMES, SYMPTOMS, SITES, AND PRIMARY BIOMARKERS

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Syndrome, Comment</th>
<th>Symptoms</th>
<th>Sites</th>
<th>Hormones/Other Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid (GI)</td>
<td>Carcinoid</td>
<td>Flush, diarrhea R. sided heart dis. Fatigue, wheeze</td>
<td>Foregut,+ Hindgut, (70%)</td>
<td>Serotonin, substance P, Neurokinin A, pancreatic peptide, urine 5-HIAA, Cg-A</td>
</tr>
<tr>
<td>* Gastrinoma</td>
<td>Zollinger-Ellison</td>
<td>Acid diarrhea, pain from gastritis, peptic ulcer disease</td>
<td>Pancreas++, duodenum (9%)</td>
<td>Gastrin, pancreatic peptide (PP), gastric acid hypersecretion, Cg-A</td>
</tr>
<tr>
<td>*Insulinoma</td>
<td>Whipple’s Triad</td>
<td>Hypoglycemia, hypercetacholinemna manifestations, Neuroglycopenia symptoms. Skin rash- Necrolytic Migratory Erythema (NME)</td>
<td>Pancreas++ (17%)</td>
<td>Inappropriate insulin in presence of low glucose (&lt;50) Ins/Glu Ratio &gt;0.3 Proinsulin, Cg-A</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Sweet’s</td>
<td>Diabetes Mellitus, Glositis, weight loss, deep vein thrombosis, altered mental states</td>
<td>Pancreas++ (1%)</td>
<td>Glucagon, pancreatic peptide (PP) Cg-A</td>
</tr>
<tr>
<td>Vipoma</td>
<td>Verner-Morrison</td>
<td>Life threatening Secretory diarrhea</td>
<td>Pancreas++ (2%)</td>
<td>Vasoactive Intestinal Peptide (VIP)</td>
</tr>
<tr>
<td>PPoma</td>
<td>Watery Diarrhea Syndrome (WDS)</td>
<td></td>
<td>Adrenal Mast Cells (very rare)</td>
<td>Pancreatic peptide, Cg-A (low K+ &amp; HC03, high chloride acidosis)</td>
</tr>
<tr>
<td>“non-functional”</td>
<td>Co-exists with other pancreatic tumours</td>
<td></td>
<td>Pancreas++ (15%)</td>
<td>Pancreatic Peptide PP, Cg-A</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>“non-functional”</td>
<td>Diabetes Mellitus, Cholelithiasis, Steatorrhea</td>
<td>Pancreas ++, Duodenum (1%)</td>
<td>Somatostatin Cg-A</td>
</tr>
<tr>
<td>Carcinoid (Broncho-pulmonary)</td>
<td>Carcinoid (very rare)</td>
<td>Cough, pain, pneumonitic, diarrhea, (rare), flush rare</td>
<td>Bronchus, lung parenchyma (25%)</td>
<td>Cg-A (predominantly) Pancreatic Peptide ACTH</td>
</tr>
<tr>
<td>Medullary Thyroid Carcinoma</td>
<td>Asymptomatic</td>
<td>Diarrhea (Sporadic MTC)</td>
<td>Thyroid (calcitonin cell) (7% of thyroid cancer)</td>
<td>Calcitonin Carciinoembryonic antigen (CEA) is a de-differentiation marker</td>
</tr>
<tr>
<td><strong>Pheochromocytoma</strong></td>
<td>Hypertensive crisis</td>
<td>Pallor, palpitations, perspiration, HA. Episodic HTM; can be constant in larger tumours.</td>
<td>Adrenal, ganglia and paraganglia</td>
<td>Free Metanephrine &amp; Nor Metanephrine Cg-A</td>
</tr>
</tbody>
</table>

*Commonly associated with known MEN 1
** Associated with MEN 2 (familial & sporadic), VHL, NF-1, all often bilateral
+ % Occurance of all carcinoid NET
++ % Occurance of all pancreatic NET
2.4.2. **Clinical syndromes**

2.4.2.1. **The carcinoid syndrome**

The carcinoid syndrome is predominantly characterized by flushing (>80%) and diarrhea (70%); it may also be accompanied by bronchial obstruction (wheezing) in some patients (17%) or symptomatic hypotension. The main hormones involved in carcinoid syndrome are serotonin and substance P (pain) in midgut tumours, less commonly in foregut NETs (10%), and rarely in hindgut (1%).

Carcinoid heart disease occurs as long-term complication of chronic hyperserotonemia in up to 40% of these patients; progressive heart disease is the primary cause of death rather than tumour progression once carcinoid heart disease becomes symptomatic.

Serotonergic crisis (for example, during anaesthesia induction or interventional procedures at the liver metastases) can be a life-threatening condition requiring immediate management with intensive care and intravenous somatostatin congeners (see below).

2.4.2.2. **Gastrinoma**

Gastrinoma is characterized by hyperacidity due to gastrin hypersecretion from a tumour of the pancreas or duodenum. More than 90% of gastrinomas are found in the gastrinoma triangle, comprised of cystic and common ducts, mesenteric vessels, and lateral portion of the duodenal C loop. The symptoms of gastrinoma are associated with peptic ulcer disease, diarrhea (70%) and reflux esophagitis. Conditions of dyspepsia, hemorrhage and abdominal pain are all due to hyperacidity. 70% to 80% of the duodenal gastrinomas are associated with MEN-1 (see 2.4.2.8. NETs and hereditary syndromes).

The wide-spread use of proton pump inhibitors (PPI) might mask many of the typical gastrinoma symptoms, therefore delaying the diagnosis for months or years. An elevated fasting serum gastrin is a typical finding of gastrinoma.

2.4.2.3. **Insulinoma**

Classical symptoms of insulinoma are expressed as Whipple’s triad: symptomatic hypoglycaemia, biochemically confirmed low blood sugar (<50 mg% or 2.6 mmol/l), and relief of symptoms by glucose ingestion. Sequelae from episodic hyperinsulnemia and/or hypoglycaemia are obesity, hypercatecholaminergic and neuroglucopenic symptoms (ranging from sweating, tachycardia to non-specific neurological symptoms, concentration disorders to focal or generalized seizure and coma or even death). More than 90% of insulinomas are benign, and almost 100% are located within the pancreas. 10% of insulinomas are associated with MEN-1, and these may be multifocal and plurihormonal.

2.4.2.4. **Glucagonoma**

Glucagonoma is characterized by necrotic migratory erythema, also associated with acquired diabetes mellitus due to glucagon hypersecreting tumour. This syndrome is very rare and has been referred to as the “4D” syndrome comprising dermatosis (80%), diabetes (80%), deep vein thrombosis (50%) and depression (50%). Additional symptoms are weight loss (90%), painful glossitis, stomatitis. Elevated glucagon levels establish the diagnosis.
2.4.2.5. **VIPoma**

Also known as watery diarrhea syndrome or Verner Morrison Syndrome, VIPoma is caused by the abnormal secretion of vasoactive intestinal peptides. This condition is characterized by severe watery (secretory) diarrhea, hypocalcemia, hypochlorhydria and metabolic acidosis. This often results in severe dehydration requiring large intravenous fluid (up to 9-10 l/day) and electrolytes replacement. Elevated vasoactive intestinal peptide (VIP) in the presence of such diarrhea and metabolic changes establishes the diagnosis.

2.4.2.6. **Rare functioning tumours**

This group may include GHRH and ACTH secreting tumours leading to acromegaly and Cushing’s syndrome, respectively. Diagnoses are established by means of appropriate endocrine function tests in the presence of a typical physical appearance.

2.4.2.7. **Non-functioning tumours**

Non-functioning tumours account for 50% to 60% of all NET. They also include NET that are clinically silent but secreting a predominant substance (e.g. PPoma). Somatostatinoma can be considered non-syndromic [33]. Non-functioning tumours are either diagnosed incidentally (e.g. by endoscopy) or due to unspecific symptoms following mass effects, such as liver enlargement, pancreatic duct obstruction or jaundice.

2.4.2.8. **NETs and hereditary syndromes**

When a NET is diagnosed in a young, less than 30-year-old patient, a familial syndrome should be suspected. Hereditary syndromes that are associated with NET include: Multiple endocrine neoplasia -1 (MEN-1), MEN-2a / MEN-2b, Von Hippel-Lindau syndrome (VHL), Neurofibromatosis-1 (NF-1), Succinate Dehydrogenase Deficiency Syndrome (SDHD-B).

MEN-1 is defined by the “3 Ps”: pituitary tumour (most common prolactinoma or non-functioning, rarely ACTH or GH secreting tumours), pancreatic neuroendocrine tumour, parathyroid hyperplasia.

Endocrine pancreatic tumours are most commonly very small (<1 cm), multifocal and plurihormonal, and most often without a clinical syndrome. The two most commonly co-associated NETs of MEN-1 are gastrinoma and insulinoma.

MEN-2a is associated with medullary thyroid cancer (MTC), parathyroid hyperplasia and catecholamine secreting adrenal pheochromocytoma. MEN2-b is without parathyroid hyperplasia. Pheochromocytomas are bilateral in up to 50% of the cases. The predominant hormone for MTC is calcitonin and CEA is considered as a tumour marker.

Von Hipple Lindau syndrome is an inherited disorder characterized by the formation of cysts benign and malignant tumours throughout the body including angioblastomas of the brain and the spinal cord, pheochromocytoma and non-functioning endocrine tumours of the pancreas.

NF-1 is associated with pheochromocytoma in 10%. Patients with germline mutations of the SDH-B or SDH D gene manifest with pheochromocytomas and paraganglioma and may display symptoms of hypertension.
A patient with a family history of endocrine pancreatic tumours or multiple endocrine tumours should be referred to genetic counseling.

2.5. Clinical course and prognosis

The clinical course of metastatic neuroendocrine tumours is highly variable and depends on the location, histopathology, including grading, somatostatin receptor expression and extent of disease (tumour stage), and growth velocity (inherent tumour biology as determined by conventional imaging) at the time of presentation.

It is not uncommon that NET are progressing slowly over years or decades and do not behave in an autonomous fashion “cancer in slow motion”, especially in midgut tumours. Even after periods of slow or moderate progression tumours may spontaneously stabilize for various periods of time.

In general, pancreatic NET tend to be more aggressive, leading to shorter median survival times [34] in an equivalently paired grading system. Spontaneous tumour remissions are extremely rare.

Prognostically negative outcome parameters include histopathological high-grade tumours, advanced tumour stage, high tumour burden, which is also co-associated by rising Cg-A levels [35] and low somatostatin receptor density by in vivo imaging [36].

Survival rates vary between countries and may be well due to the development of highly specialized multi-disciplinary tumour centers. Median survival rates are 124 months for well differentiated tumours compared to 64 months for moderately differentiated NETs and 10 months for poorly differentiated NETs, according to the ‘Surveillance, Epidemiology and End Results’ (SEER) database from 1973 to 2004, as recently published by Yao et al. [5]. According to SEER database, for the period 1988-2004 the 5-year survival rate in distant metastastic disease is 27% for pancreatic NETs and 54% for jejunal-ileal NETs. According to national databases and registries in Europe, the 5-year survival rates for the same NET subgroups of histological differentiation vary between 55% and 70% [37-41].

The overall 5-year survival rate in neuroendocrine tumours for all stages and all primary locations is about 55% [6].

2.6. Confirmation of diagnosis and staging

2.6.1. Revision of histopathology specimens

In cases of incomplete or unclear histopathological diagnosis the histological specimens should be evaluated by an experienced pathologist for revising a paraffin-fixed tumour tissue in as much as possible to confirm the neuroendocrine nature of the tumour and determine the grading, if missing. The latter is of prognostic significance, as shown by two large groups [42, 43]. If there is a time delay between initial diagnosis of the disease and presentation of the patient for decision making, it may be necessary to obtain a core biopsy. Fine needle aspiration (FNA) for this purpose cannot, however, be recommended.
2.6.2. **Biochemical assays in functional tumours**

The value of biochemical assays lies in the confirmation and the support of the clinical diagnosis and in the follow-up management and response assessment to therapeutic intervention. It may prove to be of prognostic value as well (see Table 2.4).

For confirmation and follow-up of the clinical syndromes the following markers are routinely measured in the following syndromes:

2.6.2.1. **Carcinoid syndrome**

The syndrome is confirmed with measurement of elevated 5-HIAA in 24 hrs urine or markedly elevated plasma serotonin. With most assays 5-HIAA measured by HPLC is more reliable than single measurement of circulating serotonin. It is critical to collect urine on acid, either acetic acid or HCl, according to the specific requirements of the laboratory. Dietary restrictions of serotonin-containing food should be applied. It may be useful to collect creatinine as well, if complete 24 hrs collections are not feasible [44].

2.6.2.2. **Hypoglycemia-associated syndrome (insulinoma)**

The diagnosis is established by measurement of elevated insulin and C-peptide or proinsulin (the latter, if insulin not elevated) in conditions of hypoglycemia. If insulinoma is suspected, a fasting test of up to 72 hrs with simultaneous measurement of insulin/C-peptide and glucose is the gold standard of diagnosis. Within 48 hrs 85-90 % and at 72 hrs more than 95% of the patients will develop symptomatic hypoglycaemia. The fasting test is terminated in the condition of low blood sugar (<45 mg/dl or 2.5 mmol/l) accompanied by symptoms, although after long standing repetitive hypoglycaemia symptoms may be masked. The 72 hr fasting test should be performed in the appropriate clinical setting with a patent intravenous line and with clinical monitoring of symptoms and glucose at least every 2-4 hrs and more frequently, if needed. To exclude facticious hypoglycaemia, measurement of sulfonylurea (urine or blood) and C-peptide should be considered.

2.6.2.3. **Zollinger Ellison Syndrome (gastrinoma)**

Serum Gastrin levels are usually markedly elevated in more than 90% of the patients. A single very low pH less or equal 2 in combination with elevated gastrin levels is usually diagnostic of gastrinoma. Alternative to a single pH determination, a midnight to 6 am or 24 hrs pH metry demonstrating greater than 15mEq/h gastric acid is also considered as a positive test.

Other conditions leading to isolated hypergastrinemia (in the absence of hyperchlorhydria) include renal failure, pernicious anemia and and less often gastric outlet obstruction, helicobacter pylori infection. In these instances the secretin provocation test may be required.

A secretin provocation test is performed using 2 IU/kg bolus injection of secretin and measuring serum gastrin levels at baseline (0 minutes), 10, 20, and 30 minutes after secretin injection. A delta increase of gastrin above 200 pg/ml is considered positive in 90% of cases.

2.6.2.4. **Rare endocrine pancreatic tumour syndromes**

This group comprises VIPoma, glucagonoma and somatostatinoma.
As to **VIPoma**, in the setting of the clinical syndrome, confirmation of VIPoma is made with measurement of vasoactive intestinal peptide (VIP) using EDTA tubes containing the protease inhibitor, trasylol, collected and rapidly placed on ice, spun down, separated and frozen.

In **glucagonoma** levels of plasma or serum glucagon are determined in a fasting state by means of ELISA or RIA in samples gathered using vials with the protease inhibitor trasylol (500 U/10 ml). Samples should be collected quickly on ice, spun down, separated and frozen.

**Somatostatinomas** are very rare. Measurement of plasma somatostatin is in general not recommended and very difficult to obtain commercially.
### TABLE 2.4. SUMMARY OF TUMOUR TYPE AND CORRESPONDING SECRETED SUBSTANCES (HORMONES) AND ANALYTICAL PROCEDURES

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Pred. Hormone/Substance</th>
<th>Specimen Collection Laboratory Procedures*</th>
<th>Normal Limits**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid GI and Lung</td>
<td>Cg-A (Chromogranin A)</td>
<td>EDTA-plasma, RIA</td>
<td>Depends on lab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generally</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;50mg/mL(random)</td>
</tr>
<tr>
<td>Carcinoid GI Primarily</td>
<td>Serotonin</td>
<td>EDTA-plasma &amp; ascorbic acid, HPLC</td>
<td>&lt;200ng/ml (random)</td>
</tr>
<tr>
<td></td>
<td>Substance P</td>
<td>EDTA-Plasma, RIA</td>
<td>&lt;225 pg/ml (random)</td>
</tr>
<tr>
<td></td>
<td>Neurokinin A</td>
<td>EDTA-Plasma, RIA</td>
<td>&lt;40 pg/ml (random)</td>
</tr>
<tr>
<td></td>
<td>5-HIAA</td>
<td>24hr urine collection with acetic acid, HPLC, (creatinine rec)</td>
<td>&lt;10 mg/24 hr.</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin, Gastric acid</td>
<td>EDTA-plasma, RIA</td>
<td>&lt;125 pg/ml (random)</td>
</tr>
<tr>
<td></td>
<td>pH determination of gastric acid</td>
<td></td>
<td>&gt;15meq H⁺/hr</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Insulin, Proinsulin</td>
<td>EDTA-plasma, RIA</td>
<td>&lt;24 μU/ml (random)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;20 pg/ml (random)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ins/glu Ratio &lt;0.3</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>EDTA-plasma, RIA</td>
<td>&lt;50 pg/ml (fasting)</td>
</tr>
<tr>
<td>Vipoma</td>
<td>VIP (Vasoactive Intestinal Peptide)</td>
<td>EDTA-plasma, RIA</td>
<td>&lt;50 pg/ml (random)</td>
</tr>
<tr>
<td>Ppoma</td>
<td>PP (Pancreatic peptide)‡</td>
<td>EDTA-plasma, RIA</td>
<td>&lt;225 pg/ml (random)</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Somatostatin</td>
<td>EDTA-plasma</td>
<td>&lt;20 pg/ml (random)</td>
</tr>
<tr>
<td>Medullary Thyroid Carcinoma</td>
<td>Calcitonin</td>
<td>EDTA-Plasma, RIA</td>
<td>&lt;20 pg/ml (random)</td>
</tr>
<tr>
<td>(Calcitonoma)</td>
<td>CEA, CEA-Embryonic Antigen</td>
<td></td>
<td>&lt;5 ng/ml</td>
</tr>
<tr>
<td>Pheochromocytoma paraganglieneuroma</td>
<td>Free Metanephrine, Free Nor-metanephrine</td>
<td>EDTA-plasma, RIA</td>
<td>&lt;0.50 nmoles/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.9 nmoles/L</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia Type I</td>
<td>Pancreatic tumour markers &amp; PTH, and prolactin</td>
<td>EDTA-plasma, both Immunometric Chemilluminescence</td>
<td>&lt;60 pg/ml (PTH)</td>
</tr>
<tr>
<td>N/E Mets to Liver</td>
<td>Pancreastatin</td>
<td>EDTA-plasma, RIA</td>
<td>&lt;125 pg/ml</td>
</tr>
</tbody>
</table>

* RIA – Radio immunoassay, HPLC – High Pressure Liquid Chromatography.
** Upper normal limits highly variable among laboratories. Keep within one specific laboratory when following patient.
‡ And for all non-functioning neuroendocrine tumours.
2.6.3. General tumour markers

The most important circulating tumour marker for both functioning and non-functioning NET is Chromogranin A. This is an acidic protein that resides and coexists with catecholamines within large chromaffin granules in the vast majority of neuroendocrine cells and their tumours. Cg-A belongs to a unique family of secretory chromogranins that include chromogranin B and C. It is considered a prohormone without relevant biologic function.

Cg-A is considered standard of care in many institutions for GEP NET for both determination of diagnosis and monitoring during therapy [45]. The circulating level appears to correlate with the amount of tumour burden [46] and is highly expressed and secreted in well differentiated tumours in contrast to poorly differentiated ones. A delta of 25% or more is considered a significant change in assessing successful therapy or a change of management. This, however, should always be taken in light of the association between the biochemical value and anatomic imaging.

False positive Cg-A values may be encountered in patients that have been on long-term and even short-term treatment with antacids, especially proton pump inhibitors [47], and in patients with chronic atrophic gastritis, renal and heart insufficiency, cardiovascular disease (hypertension, angina pectoris), inflammatory bowel disease and pancreatitis. Intake of proton pump inhibitors should be interrupted for at least one week and Cg-A determined again before initiating other diagnostic steps [48].

Several Cg-A assays are used with variable sensitivity and equal specificity [49]. The choice of the assay is, however, depending on the preferences of the different countries. One of the most used and distributed assays within Europe are the CisBIO and the Dako ELISA. At least five different Cg-A assays, either RIA or ELISA, are commercially available in the U.S., but only the Quest and Interscience Institute assays have been standardized. Cg-A has not been standardized within or between the countries. Therefore, and also in consideration of the variability of the different assays, it is critical and essential that the patient is monitored with the same assay and preferably the same reference laboratory.

Cg-A is not recommended to be used as a screening marker. If Cg-A is not elevated in patients with existing tumour, then alternative markers should be considered, like Neuron Specific Enolase (NSE) or Pancreatic Polypeptide (PP).

In the future other markers, such as pancreastatin, might prove useful for prognosis of liver tumour burden [50, 51]. Pancreastatin is one of the Cg-A-derived peptides with known biological inhibitory activity. It induces a general inhibitory secretory effect in many exocrine and endocrine systems.
REFERENCES


3. SPECIAL CONSIDERATION OF PRRNT IN CHILDREN AND ADOLESCENTS

3.1. Introduction

The rationale for separate discussion of neuroendocrine tumours in children and in young adults under the age of 30 is based on the following observations:

1) NETs and neural crest tumours in children express high levels of somatostatin receptors and can potentially be treated with PRRNT;

2) with the exception of appendiceal carcinoid, most neuroendocrine tumours in children are metastatic at diagnosis; and

3) children under the age of 18 have been excluded from participation in PRRNT trials resulting in a lack of information on safety, toxicity, and efficacy in this age group.

NETs arise from the diffuse neuroendocrine system. NETs are notorious for late diagnoses, often being diagnosed on the basis of liver or bone metastases [1]. The few published reports on NETs in children suggest that at least 10% of these young patients have metastatic disease at presentation [2-7]. These late diagnoses are due in part to the wide distribution of the diffuse neuroendocrine system [8] and to the multiple histologic diagnoses associated with NETs [9]. According to the SEER database, every neuroendocrine tumour observed in adults also occurs in children. However, epidemiology of NETs, especially those extracted from the SEER database studies, includes several neural crest tumours, as outlined in the table below.

TABLE 3.1. TUMOUR TYPES IN CHILDREN ACCORDING TO HISTOLOGICAL ORIGIN

<table>
<thead>
<tr>
<th>Diffuse Neuroendocrine System Tumours</th>
<th>Neural Crest Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary carcinoma (breast and thyroid)</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Small cell and large cell carcinoma (ovary and cervix)</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td>Neuroendocrine Tumour / Neuroendocrine Carcinoma including carcinoid</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Islet Cell Tumours</td>
<td>Ewing’s Sarcoma</td>
</tr>
</tbody>
</table>

3.2. Epidemiology

Patients who are eventually diagnosed with neuroendocrine tumours often have a multi-year history of symptoms prior to identification of the malignancy with average lag periods of 8-10 years [10]. Thus, a 29-year-old adult diagnosed as having a NET may well have been an adolescent when the first symptoms occurred. The incidence increases with age and nearly 90% of NETs in the 0-29 years age group are diagnosed over the age of 20. However, the tendency to late diagnosis, after metastases to the liver or bones, suggests that more than half of NETs diagnosed in this age group probably occur prior to the age of 21.
The incidence of neuroendocrine tumours in children and young adults in the U.S. has recently been analyzed using long-term follow-up information provided by SEER ‘Surveillance, Epidemiology and End Results’ database. Incidence rates, observed survival rates, and the 31-year limited duration prevalence counts were obtained from SEER for diagnosis years 1975 to 2006 [11]. These rates were compared between and within NETs using variables from 9 standard SEER registries for ages 0-29 years. The most common NET sites were lung, breast, and appendix with incidence rates of 0.6 for lung, 0.6 for breast, and 0.5 per million for appendix in the age group 0 to 29 years. Incidence was less than 0.1 per million for all other neuroendocrine tumours. The estimated age-adjusted number of NETs in the United States was 1073 in 2006. NET five-year observed survival rates were 84% for the 2000-2006 period, and the estimated 31-year limited duration prevalence for NETs as of January 1, 2006 was 7724. The age-adjusted multivariate Cox Regression demonstrated small cell histology, primary location in the breast, and distant stage as major predictors of decreased survival with 5 year survival of <24% for ovarian small cell NET.

3.3. Tumours in children eligible for PRRNT

3.3.1. Carcinoid (neuroendocrine tumour)

The lung is the most common location for NET in young people, and NET is the most common childhood malignancy arising in the lung [12]. NETs should be considered in any young person who has a culture negative pneumonia and especially in the case of recurrent, culture negative pneumonia; a chest CT should be performed, and if a lung lesion is found, a biopsy should be obtained. NET biomarker levels (Cg-A, serotonin) should be measured in these children before surgery in order to determine biomarkers to be utilized in followup.

The gastroenteropancreatic NETs together constitute another major site for NETs in children, with appendix and pancreas being most frequent sites. Both functioning and non-functioning pancreatic neuroendocrine tumours occur in children. Biomarkers are also useful in diagnosis and followup of these tumours, as a specific marker may indicate the likely location of the primary (e.g. gastrin, insulin, glucagon, substance P, neurokinin A) or to follow liver metastases (pancreastatin). Gastrinoma has been reported as early as six years of age [7]. Normal fasting gastrin levels are similar in children and adults, making this an easy and extremely useful test. However, even short-term use of proton pump inhibitors (PPI) medication can significantly raise gastrin and Cg-A levels. PPI should be discontinued for at least 72 hours before measuring neuropeptide levels in serum, and some patients may require up to 4 weeks off PPI to allow for peptide levels to return to normal [13].

Neisidioblastosis is the result of an overactive pancreas (hypertrophy and hyperplasia of the islet cells) and most often presents at birth as hypoglycemia unresponsive to feeding or IV glucose. This most often resolves with close followup and Octreotide therapy, but may resurface when these children reach puberty [14]. Insulinoma has been seen in children as young as five years of age [15-19]. Insulin and C-peptide levels are measured in blood, and normal levels are similar to adults.

Gastroenteropancreatic NETs have high somatostatin receptor expression and have an excellent [20] response to PRRNT [21]. PRRNT may render previously unresectable tumours amenable to surgery. Whether PRRNT should be the initial therapy followed by surgery and/or chemotherapy such as temozolomide and capecitabine, must be decided on an individual basis.
3.3.2. Medullary carcinoma

Medullary carcinoma occurs more often in breast than in thyroid in this age group; the primary lesion is often found by the patient, but primary breast location should also be considered in the case of metastatic disease to bone that is found on pathology to be medullary carcinoma. These tumours could be considered non-functional, as none of the usual neuroendocrine tumour markers are useful. Surgical excision with clear margins is the treatment of choice [22]. PRRNT would only be indicated if residual tumour or metastatic disease were found on Octreotide scintigraphy.

3.3.3. Multiple endocrine neoplasia

Multiple endocrine neoplasia (MEN-1) occurs in parathyroid, pancreas and pituitary. MEN-2a occurs in parathyroid, thyroid (medullary thyroid carcinoid, MTC) and adrenal medulla (pheochromocytoma), while MEN-2b includes MTC, pheochromocytoma and neural crest tumours. Family history and blood pressure measurements are the most important screening tools. Children can be tested and diagnosis made as early as 4 years of age with blood calcitonin levels; the pentagastrin stimulation test is available, but rarely performed. Urine catecholamines are also important and require 24 h urine collection. Plasma metanephrine measurement is an alternative in young children for whom 24 h urine collection is nearly impossible. Recommendation for thyroid removal is dependent upon the family history and the precise characteristics of the RET mutation [23, 24]. PRRNT would only be considered if the primary tumour and any metastatic lesions were positive on $^{111}\text{In}$-DTPA-Octreotide SPECT scan.

3.3.4. Munchausen’s syndrome by proxy

Diarrhea, flushing, sweating, fatigue are hallmark symptoms of neuroendocrine tumours; however, each of these symptoms is common in normal, healthy children associated with viral infections, topical exposures, and allergies. A parent, relative, or guardian can easily induce such symptoms in the child. For instance, fictitious, iatrogenic diarrhea can be induced with laxatives and should be included in the screening process. Ricins cause overall irritation of the gastrointestinal tract, whereas castor oil will induce vomiting as well as some gastrointestinal upset. These can be measured in the stool along with pH and stool electrolytes.

3.3.5. Neuroblastoma

This neural crest tumour shares multiple biomarkers with neuroendocrine tumours, including Cg-A, synaptophysin, neuron specific enolase, and sstr2 [21]. 90% of all neuroblastomas can be imaged with either $^{111}\text{In}$-DPTA-Octreotide or $^{68}\text{Ga}$-DOTA-Octreotate [25, 26], supporting the use of PRRNT in treatment of neuroblastoma. Individual case studies validate this theoretical consideration, including minor responses in two subjects with neuroblastoma who participated in a Phase I trial of $^{90}\text{Y}$-DOTA-tyr$^3$-Octreotide in children [21]. Diagnostic testing should include vanillylmandelic acid and homovanillic acid (VMA/HVA) in urine, serum Cg-A, and either SPECT/CT or PET/CT to localize sstr2 positive disease.

3.3.6. Pheochromocytoma and paraganglioma

Pheochromocytoma is associated with MEN 2a and 2b, von Hippel-Landau (VHL) syndrome, and neurofibromatosis (NF1). With the peak incidence between 9 and 12 years of age, nearly 10% of all pheochromocytomas occur in children, and 10% of these are malignant.
Headaches, palpitations, diaphoresis, and hypertension are the most common symptoms. Diagnostic testing should include 24 hour urine for creatinine, VMA, catecholamines and metanephrine as well as free plasma metanephrine and Cg-A. Since pheochromocytoma can be seen in adolescents and young adults, drug interference with metanephrine testing should be ruled out with a careful medication and illicit drug history. False positive metanephrines can be caused by buspirone, benzodiazepines, methyl dopa, labetalol, tricyclic antidepressants, levodopa, ethanol, amphetamines, sotalol, and chlorpromazine. Those pheochromocytomas and paragangliomas that are positive on $^{111}$In-DPTA-Octreotide scan may be amenable to PRRNT [27].

3.3.7. Small cell carcinoma

Small cell carcinoma of cervix and ovary is more common in children and young adults than small cell carcinoma of lung; ovarian small cell carcinoma can be familial [28, 29] and has a poor prognosis. There is very little information on sstr2 expression in these tumours and thus, the use of PRRNT must be based on positive sstr2 SPECT or PET imaging.

3.4. Administration of PRRNT in children and young adults

Only one controlled clinical trial of PRRNT has ever been conducted in children and young adults; this was a Phase I trial of $^{90}$Y-DOTA-tyr$^3$-Octreotide to determine the dose-toxicity profile in subjects under the age of 25 years with somatostatin receptor positive tumours [21]. A dose escalation design was utilized to determine highest tolerable dose of $^{90}$Y-DOTA-tyr$^3$-Octreotide while limiting the permitted renal radiation dose in this study to $\leq 21$ Gy. Activity levels of administered $^{90}$Y-DOTA-tyr$^3$-Octreotide were 1.11, 1.48 and 1.85 GBq/m$^2$/cycle in 3 cycles at 6-week intervals, co-administered with an amino acid infusion for renal protection. Eligibility criteria included age 2-25 years, progressive disease, positive lesion on $^{111}$In-DTPA-Octreotide scan, glomerular filtration rate $\geq 80$ ml/min/m$^2$, bone marrow cellularity $\geq 40\%$ or stored autologous hematopoietic stem cells, Lansky Play Scale $\geq 60\%$, and informed consent.

Seventeen subjects, ages 2 to 24 years, received at least one dose of $^{90}$Y-DOTA-tyr$^3$-Octreotide; diagnoses included neuroblastoma, embryonal and astrocytic brain tumours, paraganglioma, MEN-2B, and gastroenteropancreatic NETs. There were no dose limiting toxicities and no individual dose reductions due to renal or hematologic toxicity. The most frequent toxicity was reversible nausea in 70%, even in the presence of antiemetics. There were no complete responses; 3 subjects experienced partial response (PR), 5 had minor responses (MR), 5 experienced stable disease (SD), 2 had progressive disease (PD) and 2 subjects withdrew. Dosimetry performed on subjects in the 1.85 GBq/m$^2$/cycle cohort demonstrated an average 2.24 mGy/MBq dose to kidneys, similar to the dosimetry estimates in adults. PRRNT with $^{90}$Y-DOTA-tyr$^3$-Octreotide demonstrated an 18% PR plus 29% MR rate in children and young adults with somatostatin receptor positive tumours. The recommended Phase II dosing is three cycles of 1.85 GBq/m$^2$/dose $^{90}$Y-DOTA-tyr$^3$-Octreotide co-administered with amino acids. In the future, higher doses may be attainable through the use of dosimetry-guided therapy.

3.5. Teaching points

Though there has been only one clinical trial in children, the observations in that trial of $^{90}$Y-DOTA-tyr$^3$-Octreotide together with the combined experience of several centers using $^{177}$Lu-
Octreotate in children and young adults allow us to offer several recommendations for PRRNT in this age group:

1. PRRNT is safe in children and young adults when given with renal protection.

2. Dosing of $^{90}$Y-DOTA-tyr$^3$-Octreotide is recommended at 1.85 GBq/m$^2$ in all children and in young adults <1.73 m$^2$. Dosing of $^{177}$Lu-Octreotate is currently recommended at 7.4 GBq/m$^2$.

3. Total irradiation dose to kidneys should be limited to 23 Gy until further controlled trials have been performed to demonstrate safety at higher doses.

4. Renal protection with amino acid infusion 30-60 min prior to and at least 3½ hrs after PRRNT administration is mandatory. Recent trials suggest that such protection should be continued for 24-48 hrs following PRRNT administration [30].

REFERENCES


4. ANATOMIC IMAGING

4.1. Introduction

Anatomical imaging of neuroendocrine tumours should be as detailed and extensive as possible to provide accurate information concerning site and extent of primary tumours and the localization and extent of regional and distant metastases. Ideally, procedures such as somatostatin receptor scintigraphy combined with an exact radiological examination for the staging of tumours are preferable. In addition, serial radiological examinations are essential for monitoring therapy and the detection of recurrent disease.

4.2. Endoscopy, ultrasound, and endoscopic ultrasound

Endoscopy is essential for detection and histological sampling of enteral and bronchial NETs. Neuroendocrine tumours of the stomach and rectum are often found incidentally. The role of pull-and-push endoscopy and capsule endoscopy for the detection of neuroendocrine tumours of the ileum and jejunum is less clear, since these tumours are often small and may arise from the submucosa.

Ultrasound is the most widely available imaging technique. This technique is operator-dependent and provides a wide range of sensitivity and specificity [1]. In primary pancreatic NETs, conventional ultrasound shows a mean detection rate of 39% (range 17-79%), and a sensitivity of 18% for duodenal tumours and lymph node metastases. Detection rates for liver metastases of NETs are higher; 88% sensitivity and 92% specificity have been reported [2]. Application of contrast material applying contrast enhanced ultrasound (CEUS) may further increase sensitivity and specificity [3, 4].

Endoscopic ultrasound is the most sensitive method to detect pancreatic and duodenal tumours and is essential as well for the exact staging of primary tumours of the upper or lower gastrointestinal tract (e.g. NETs of the stomach or rectum). The method has a mean detection rate of 90% (range 77-100%) for pancreatic NETs has been reported in a compilation of 10 studies comprising 261 patients and is thus in the same range as intraoperative ultrasound with a mean detection rate of 92% (range 74-96%) in 4 studies with 127 patients [1]. Endoscopic ultrasound is also useful for obtaining histological specimens from lesions in or adjacent to the upper or lower gastrointestinal tract, for instance, pancreatic masses, with high diagnostic yield [5]. Endoscopic ultrasound is the preferred method for surveillance of pancreatic lesions in patients with multiple endocrine neoplasia [6].

Assessment and documentation of tumour progress is difficult with ultrasound; therefore this method is not recommended for thorough staging and clinical trials. However, ultrasound has many advantages in a clinical setting allowing a dynamic and focused examination and is especially useful in skilled and experienced hand when radiation exposure is an issue, most applicable for patients with slowly progressing tumours, in young patients, or in the rare case of monitoring tumour load during pregnancy.

4.3. Computed tomography and MRI

Radiological assessment of NETs should be as exact as possible with the lowest radiation dose. Computed tomography (CT) and magnetic resonance imaging (MRI) are widely applied worldwide. Choice of preferred imaging modality depends on local expertise, availability, side effects of contrast materials, and costs. In addition, imaging modalities should be kept
constant during follow-up of the patient to allow direct comparison of repeated testing. Care should be undertaken to perform radiological assessment according to current and local standards of imaging. It is fundamental to acquire multiple phases with special attention to the arterial phase [7, 8]. Exact assessment of liver metastases and degree of liver involvement is fundamental to define prognosis, evaluate response to treatment and to select suitable locoregional therapy.

Most radiology departments use multidetector CT scanners allowing fast and accurate imaging and reconstruction in different planes. In addition, several contrast enhanced phases may be acquired by these modern scanners. Detection rates for CT have been compiled in a recent guideline of standards of care [1], a concise summary of which is provided as follows. For the diagnosis of pancreatic endocrine tumours the sensitivity and specificity in 162 patients of CT with adequate contrast material are 73% and 96% respectively [1]. Liver metastases are detected with a mean sensitivity of 82% and specificity of 92% in a compilation of 4 studies with a total of 135 patients. In another study, more than 30% of lesions were found during the arterial phase and 6% of the hepatic metastases were detected only on the arterial phase of contrast enhanced CT [7]. Extrahepatic abdominal soft tissue metastases are diagnosed with a sensitivity of 75% and specificity of 99% in 4 studies with 135 patients. Different metastases in the thorax and abdomen are diagnosed with a sensitivity of 83% and specificity of 76% in 164 patients in 3 studies or with a detection rate of 76% in 25 patients. Enteroclysis with CT has a low sensitivity for neuroendocrine tumours in a study of 8 patients, but better results with a sensitivity of 85% and specificity of 97% have been reported in a study on 219 patients with small bowel tumours including 19 NETs [1].

Less data are available for sensitivity and specificity of MRI in diagnosis of neuroendocrine tumours. Endocrine pancreatic tumours are visualised with a sensitivity of 93% and specificity of 88% in a series of two studies including 54 patients. Reported detection rates are 73% in 192 patients in five studies. Liver metastases of neuroendocrine tumours are detected by 82% (74 patients in three studies). Dynamic contrast-enhanced MRI depicted typical hypervascular pattern in 73% of patients with the greatest number of metastases detected during hepatic arterial phase [8]. Extrahepatic abdominal soft tissue metastases are diagnosed with 89% sensitivity and 100% specificity in one study with 34 patients [1]. Although both CT and MRI can detect liver metastases, there is evidence that MRI can detect more lesions than CT [8].

REFERENCES


5. MOLECULAR IMAGING

5.1. Introduction

Radiopharmaceuticals for the imaging of the expression of somatostatin receptors (sstr), their density and subtype/s utilize either single photon emission tomography (SPECT) or positron emission tomography (PET) techniques. However, PET technique is being increasingly used for diagnosing, staging and prognosticating patients with NET. The use of dual modality image fusion of PET or SPECT with CT to provide anatomical localization of receptor-expressing lesion or their metabolic behavior (by means of $^{18}$F-FDG) allows improved patient specific, and tailored therapy design. This chapter covers the role of molecular imaging using SPECT and PET/CT in the management of patients with NETs.

5.1.1. Somatostatin analogues withdrawal

Somatostatin analogues are available as short acting or long acting preparations. These should be discontinued prior to somatostatin receptor imaging either with SPECT or PET techniques, as they might interfere with receptor targeting. The duration of interruption, however, depends on the half-life of the analogue used. A period of 3-4 weeks for long-acting release formulations and of at least 24 hours for short acting formulations is considered as good clinical practice. This topic is still a matter of ongoing debate.

5.2. SPECT imaging of NET

5.2.1. $^{111}$In-OctreoScan®

The abundance of somatostatin receptor sstr expression on NET has resulted in the development of several radiopharmaceuticals that are directed toward these sites. Among the five different sstr subtypes known, most NET express sstr2, with a low percentage expressing sstr3 and sstr5 [1]. It was introduced in diagnostic arena in 1990s using indium-$^{111}$-pentetreotide (OctreoScan®; Mallinckrodt Medical, Petten, the Netherlands). At present, in patients with NET, OctreoScan® is a major diagnostic instrument, with a more evident clinical role in subjects with gastrinoma, glucagonoma, vipoma and carcinoids [2]. Useful information, which can be integrated with other diagnostic procedures, can be obtained in patients with other tumours, such as paraganglioma, medullary thyroid carcinoma, neuroblastoma and small cell lung cancer (SCLC). The reported sensitivity of OctreoScan® in detecting metastases is high (around 90%) with similar high specificity and diagnostic accuracy [3]. OctreoScan® demonstrated a lower sensitivity in detecting liver metastases compared to MRI and CT scan, due to its lower spatial resolution. Nevertheless, OctreoScan® is able to explore the whole body and to give therapeutic indications [4].

5.2.2. $^{99m}$Tc-HYNIC-TOC

$^{99m}$Tc-based somatostatin receptor scintigraphy holds great promise for detecting primary tumours and metastases. The prototype is $^{99m}$Tc-EDDA/HYNIC-octreotate, delivers high quality images this providing an excellent alternative to $^{111}$In-OctreoScan® [5].

5.3. PET-CT imaging of NET

PET radiopharmaceuticals can be directed toward assessing receptor expression or characterizing the intra-tumoural metabolic processes. The metabolic pathways and receptor targets that are currently being examined by PET are described in the table 5.1.
TABLE 5.1. RADIOPHARMACEUTICALS FOR PET IMAGING [6-8]

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Receptor, Metabolic pathway</th>
<th>Indication and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>18</strong>F-FDG</td>
<td>Glycolytic pathway</td>
<td>All NETs. Global sensitivity in detecting NET is low. Useful for undifferentiated NET. Observation of flip-flop mechanism with SMS-R PET</td>
</tr>
<tr>
<td>68Ga-DOTA-NOC</td>
<td>Somatostatin receptor analogue (high affinity to subtypes sstr2, 3, and sstr5)</td>
<td>All sstr positive NETs</td>
</tr>
<tr>
<td>68Ga-DOTA-TOC</td>
<td>Somatostatin receptor (high affinity to sstr2, 3, and 5)</td>
<td>All sstr positive NETs</td>
</tr>
<tr>
<td>68Ga-DOTA-TATE</td>
<td>Somatostatin receptor analogue (highest affinity for sstr2)</td>
<td>All sstr positive NETs</td>
</tr>
<tr>
<td>11C-5-HP</td>
<td>Serotonin production pathway</td>
<td>All serotonin-producing NETs</td>
</tr>
<tr>
<td>18F-DOPA</td>
<td>Dopamine production / metabolism</td>
<td>Pheochromocytoma, paraganglioma, neuroblastoma, glomus tumours</td>
</tr>
<tr>
<td>18F-FDA</td>
<td>Catecholamine precursor uptake, conversion to norepinephrine and vesicular storage</td>
<td>Pheochromocytoma, paraganglioma, neuroblastoma</td>
</tr>
<tr>
<td>64Cu-TETA-octreotide</td>
<td>Somatostatin receptor</td>
<td>All sstr positive NETs</td>
</tr>
</tbody>
</table>

5-HTP: 5-hydroxy-L-tryptophan, FDOPA: 131I-L-dihydroxyphenylalanine, 18F-FDA: 6-[18F]Fluorodopamine

5.3.1. 68Ga-PET/CT for somatostatin receptor imaging

The currently used somatostatin radiopharmaceuticals are derivatives of octreotide and, to a much lesser extent, lanreotide, and show variable binding to sstr. 68Ga-DOTA-TOC was the first radiopharmaceutical used for PET imaging of NET [9, 10]. Wild and colleagues have shown that the compound 68Ga-DOTA-NOC has three to four times higher binding affinity to sstr2, 3, and 5 than 68Ga-DOTA-TOC, which results in detection of a wide range of SSR-positive tumours (pan-somatostatin analog) and has a significant effect on diagnosis, staging, and therapy of NET and various other somatostatin-receptor expressing tumours [11-13]. The sensitivity, specificity and diagnostic accuracy of imaging agents using 68Ga-DOTA peptides is high (97, 92 and 96%, respectively) and provide superior results compared to OctreoScan® and CT scan [11]. Moreover, imaging with 68Ga-DOTA peptides demonstrated to have a clinical impact by by brining about a modification of the clinical stage or of the treatment strategy in more than 55% of 90 NET patients [14].
5.3.2. $^{18}$F-FDG

One of the fundamental energy sources of any tumour is glucose. $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$F-FDG) targets the glycolytic pathway, the main source of energy in tumours. FDG enters the glycolytic pathway like glucose in the cytoplasm, where it is phosphorylated by the enzyme hexokinase to FDG-6-phosphate. The latter molecule does not undergo further metabolization; however, it gets trapped and accumulates inside the neoplastic cells. In spite of its wide use in oncology, patients undergoing screening or diagnostic workup for a suspicious mass e.g. a solitary pulmonary nodule; $^{18}$F-FDG PET is frequently negative in patients with well differentiated NET [15, 16]. Indium-111 labeled OctreoScan®, and other better tracers namely, $^{99m}$Tc-HYNIC-TOC or $^{68}$Ga-DOTA-conjugated peptides (like DOTANOC, DOTATATE and DOTATOC), provide a reliable second-line diagnostic tool to improve overall diagnostic accuracy. Recently, despite its low diagnostic sensitivity, $^{18}$F-FDG PET was demonstrated to have a strong prognostic value. In a prospective study on 98 patients, a SUVmax of >9 and a high Ki67 index were significant predictors of overall survival, while a SUVmax of >3 was the only predictor of progression-free survival [17].

5.3.3. $^{18}$F-DOPA

NETs are characterized by the production and storage of several biogenic amines. One tracer with a design based on this observation is $^{18}$F-labelled L-dihydroxyphenylalanine ($^{18}$F-DOPA). $^{18}$F-DOPA is an aromatic amino acid labelled with fluorine-18 that was first used for the assessment of patients who have Parkinson’s disease. Belonging to the APUD (amine precursor uptake and decarboxylation) cells system, a high proportion of NET cells avidly take up $^{18}$F-DOPA and can therefore be visualized by $^{18}$F-DOPA-PET scans. Recent studies have demonstrated increased L-DOPA decarboxylase activity in 80% of NET, and it has been suggested that this could be used as a marker of tumour activity, particularly in so-called carcinoids. Nevertheless, it has been demonstrated that imaging with $^{68}$Ga-DOTA-conjugated peptides is superior to that of $^{18}$F-DOPA, which could be considered a second choice exam. Moreover, imaging with $^{68}$Ga-peptides guides therapeutic indications for applying PRRNT [8, 18-20].

5.4. Other molecular targets

New tracers are being developed to target additional G-Protein coupled receptors, including the glucagon-like-peptide–1 receptor (GLP1-R), gastrin releasing peptide receptor (GRP-R), melanocortin receptor (McR), and vasoactive intestinal polypeptide receptor (VIP-R) [21-24]. Like somatostatin analogues, these peptide ligands must be designed to have improved stability in serum and to accommodate a metal chelator such as DOTA, TETA or ETA.

Receptor antagonists constitute another class of tracers now undergoing development [25, 26]. Antagonists for the GRP and somatostatin receptors have been successfully tested in animal models and are currently in early human trials [27].
REFERENCES


6. OPTIONS OF CARE FOR NET

The following chapter discusses options of care for patients who are affected by either local, regional, or distant neuroendocrine tumour metastases. Neuroendocrine tumours of the gastroenteropancreatic system (GEP) most often metastasize to the liver. The ultimate goal of therapy is to preserve viable liver tissue for as long as possible. These tumours may remain clinically silent until a significant liver tumour burden has occurred. Further, each of the therapeutic options discussed below is not mutually exclusive and, for the most part, they are interchangeable. In the hands of an experienced multi-disciplinary team these options can be associated with a high-benefit to low-risk ratio and extended quality of life.

6.1. Role of surgery in neuroendocrine tumours

The optimal management of neuroendocrine tumours (NETs) is early surgical removal prior to vascular or lymphatic invasion, transmural extension, and the subsequent development of regional or distant metastases. Unfortunately, a large proportion of the patients are diagnosed with metastatic disease thereby ruling out radical surgical approach. The decision on surgical intervention is often complex, and must take into account various factors as the patient’s condition, the extent of the disease, and potential risks versus possible benefits of surgical exploration.

If tumour/s extension is limited or localized, then segmental resection with removal of the regional nodes is beneficiary and is indicated. Removal of the primary tumour is indicated to prevent complications such as bleeding, small bowel obstruction, and is also indicated to prevent desmoplastic reaction\(^1\) even in advanced disease. The removal of the primary tumour is associated with positive impact on survival even in the presence of metastases [1, 2]. Unoperable tumours of the pancreas can be rendered operable by means of repeated cycles of PRRNT, an example hereto is provided in FIGs 7.5 and 7.6. For tumours arising in the small bowel, resection of the affected segment should include lymph nodes leading up to the trunk of the superior mesenteric artery (SMA). A situation that arises not infrequently in small bowel NETs is that the nodal involvement might extend to the root of the SMA. Here it might be very difficult to remove the higher involved lymph nodes without compromising the arterial blood supply to the entire small bowel. This means that at least ~30 cm of small bowel will be removed if there is a single tumour. It should be remembered, however, that many patients have multiple small bowel tumours, and careful palpation of the entire small bowel should be carried out prior to resection. All identifiable lesions with their corresponding nodes should be resected, which, on occasion, may require that >100 cm of small bowel be removed. In these cases, careful measurement of total small bowel length to ensure sufficient residual absorptive surface, in addition the preservation of the ileocecal valve, where possible, is important. Trans-serosal extension of the tumour is a risk factor for disseminated intra-peritoneal spread of tumour, so careful examination of the peritoneal lining and intra-abdominal organs should be carried out; if manageable, excision of these peritoneal nodules may be performed.

\(^1\) The term refers to a tumour-associated growth of fibrous or connective tissue.
In cases of non-ruptured appendiceal carcinoid tumours, if they are less than 1 cm in diameter and do not extend trans-serosally, then simple appendectomy is an adequate treatment. When these tumours are greater than 2 cm, then ileocolectomy and node dissection should be performed. Tumours 1-2 cm in size or those with trans-serosal extension are more of a gray area, but we lean towards ileocolectomy in these cases as well, especially in younger patients in whom missing nodal metastases could inevitably result in liver metastases and shortened survival [3, 4].

Gastric NET may develop in response to hypergastrinemia, such as seen in atrophic gastritis and pernicious anemia (Type 1 gastric carcinoids). They may also be seen in patients with celiac disease. These tumours are often small with little risk of metastases, and can be excised locally or endoscopically. Type 2 gastric carcinoids occur with MEN-1 due to gastrinoma and chronic hypergastrinemia. The primary goal is to locate the tumour source (either duodenal or pancreatic) and excise it. In contrast, Type 3 gastric neuroendocrine tumours are sporadic in nature, and occurring in the absence of hypergastrinemia; they tend to be larger and aggressive. Surgical removal according to endocrine surgery standards (including subtotal gastrectomy) is indicated [5, 6].

Duodenal NET, if small (<1cm), are usually removed endoscopically. Larger tumours (>1-2 cm) do have a propensity for nodal and distant metastases, and therefore duodenectomy with nodal dissection, or in cases of invasion duodenal resection are indicated [7].

Rectal NET are also often small (<1 cm) and benign, and are mostly endoscopically removable. Larger tumours amenable to surgery will be treated by local excision; wide resection is very rarely indicated in larger or G3 tumours. Colonie NET are less common and usually larger, necessitating segmental colonic resection with node dissection [8].

Pancreatic NET located in the body and tail of the pancreas can be resected by distal pancreatectomy, commonly performed with splenectomy. Nodes along the splenic artery should be removed, as well as perisplenic and celiac nodes. Tumours in the head of the pancreas will, whenever possible, be enucleated; larger tumours generally require pancreateicoduodenectomy with removal of portocaval and aortocaval nodes. In the case of MEN-1 setting, where multiple adenomas (mostly benign and slowly growing) are the rule, consideration not to resect should be given. Functional tumours represent an exception, where surgery is indicated [9].

A frequent dilemma is the optimal management of a primary tumour with liver metastases, a condition that occurs in approximately 60-80 % the cases. Because of the relatively indolent course of many NETs, removal of the primary tumour alongside with debulking of liver metastases has several potential advantages. One is that removal of the primary may prevent the additional metastatic seeding. Second, the debulking of liver lesions may improve tumour-associate hormone secretory symptoms as their serum levels can be reduced [10, 11]. Third, reducing the number of potential sites taking up the radiolabelled somatostatin analogues or other therapies may improve the “kill” in the remaining tumour. And fourth, it appears that patients receiving liver-directed treatment alongside with removal of the intestinal primary survive longer than those not undergoing surgery or removal of the primary alone [1, 12]. Prospective randomized trial on the impact of removal of the primary tumour and/or metastases are, however, lacking.

There are several options for debulking or removal of liver metastases. Resection may be indicated for solitary lesions, or when a few lesions are localized to one lobe of the liver,
although some would argue for a more aggressive approach. Surface lesions can be enucleated relatively easily, as the tumours tend to be firm within the relatively softer parenchyma. Furthermore, they often do not recur despite the presence of tumour at their margins. Another effective debulking option is radiofrequency ablation when there are many lesions, or several large lesions. If the lesions are small and diffuse, then treatment of just a few lesions will not achieve significant hormonal relief, and therefore other postoperative strategies should be employed, such as embolization, chemoembolization, or $^{90}$Y labelled microspheres [13].

Another important adjunct to surgical exploration for NET is cholecystectomy. Most of these patients will receive adjuvant somatostatin analogue treatment, often given chronically on a monthly basis (such as Sandostatin LAR or Lanreotide Autogel). This treatment predisposes patients to develop gallstones, and therefore prophylactic cholecystectomy allows these individuals to be spared from biliary colic later in the course of their disease.

In patients presenting with metastatic disease with an unknown primary tumour, the decision to surgically explore depends on whether or not there is a reasonable notion where the primary tumour might be and the medical need or urgency to locate it (e.g. insulinoma).

### 6.2. Role of somatostatin analogues

Octreotide and Lanreotide are somatostatin receptor agonists that play an essential role in the disease control of both symptomatic and asymptomatic neuroendocrine tumours. These drugs should be considered as first-line therapy.

The first somatostatin receptor agonist described was Octreotide acetate (SMS 201-995, Sandostatin®) in 1980 by Peter Marbach. It was clinically approved in Europe in the fall of 1988 and in the U.S. in 1989. The approved indications for Sandostatin in the U.S. at the time of the FDA approval and in Europe were for the diarrhea and flushing of carcinoid syndrome and the Watery Diarrhea Syndrome of Vasoactive Intestinal Peptide (VIP) secreting tumours. More recently, lanreotide was introduced in the European market for symptomatic treatment of carcinoid syndrome, but not yet in the U.S.

Both drugs are also approved for growth hormone secreting pituitary tumours with acromegaly in adults, and gigantism in children and adolescents.

### 6.3. Molecular basis for somatostatin analogues action

More than 90% of well differentiated NETs express the somatostatin receptor subtype 2 (sstr-2). The rationale for somatostatin receptor agonist or analogues (SSA) use for symptomatic control rests with the fact that virtually all of the target cells of the tumour (e.g. secreting endocrine cells, cutaneous vessels) also express sstr-2. In addition, symptomatic control can be exerted via binding of the analogue to the sstr-5 at higher dose of octreotide.

The biological effects of SSA are probably mediated by a family of G protein-coupled receptors that are expressed in a tissue-specific manner. Binding of SSA to sstr-2 and sstr-5 exerts inhibitory effects on cellular signal transduction pathways through the inhibition of cyclic AMP production. This in turn leads to the inhibition of amine and peptide secretion and cellular proliferation, and a more complex pathway, involving several mechanisms, to the induction of apoptosis [14]. Somatostatin analogues are widely used in the USA and Europe for both symptomatic neuroendocrine tumour control and for non-symptomatic
neuroendocrine tumours. The biological effects of somatostatin are probably mediated by a family of G protein-coupled receptors that are expressed in a tissue-specific manner.

6.4. Antisecretory treatment

6.4.1. Carcinoid syndrome

Somatostatin analogues (SSA) are used to treat the symptoms of the carcinoid syndrome, such as flushing and diarrhea or bronchial obstruction. It is reported that they control the clinical syndrome in 40-90% of the cases depending on tumour load and dosages [15, 16].

However, a frequent observation is a “breakthrough” of symptoms following 1-2 years on treatment with SSA e.g. octreotide or lanreotide. Patients may become medication refractory with regards to syndrome control due to tachyphylaxis i.e. the loss of tumour sensitivity to treatment with sstr-analogues expressed through the lack of exerting inhibition on growth responsible signal transduction pathways, or due to tumour progression. With increase of the SSA dose, better symptom control may be achieved again.

Rescue treatment is the term use for subcutaneous injection of short-acting formulation that can be useful for patients under treatment with the long acting analog Sandostatin-LAR®. For Lanreotide Autogel® no short acting formulation is available.

Tumour progression, however, requires in most cases an additional treatment including use of PRRNT.

6.4.2. Prevention and therapy of carcinoid crisis

In patients with carcinoid syndrome, octreotide is used for prevention of carcinoid crisis that is a life-threatening complication induced by excess serotonin and other mediator secretion in the circulation. It is a standard procedure to use octreotide peri-operatively and during induction of general anaesthesia. If the patient is not on a depot formulation, a bolus of 200-500 µg octreotide is given 1x day prior to surgery or on the day of surgery. This is followed by continuous intravenous infusion of octreotide at a rate of 50-100 µg/hr starting prior to surgery and continued one day following surgery. Higher amounts of octreotide may be needed depending on the tumour burden and the degree of hormaonal secretion (functionality) [17].

6.4.2.1. Octreotide medication in endocrine pancreatic tumours

Endocrine pancreatic tumours (EPT) comprise gastrinomas, VIPomas and glucagonomas have a high density of sstr-2. In VIPomas octreotide reduces serum levels of viasocative intestinal peptide (VIP) in greater than 80% of patients and improves diarrhea in greater than 75%, but the response is often short-lived (<1 y) if dose is not increases. In glucagonomas, octreotide decreases plasma glucagon levels in greater than 80% of the patients and improves migratory necrolytic erythema in 90% while complete resolution can be achieved in 30%. Octreotide is not recommended for hormonal control of gastrinoma as first-line therapy, as the therapy with proton pump inhibitors (PPI) is efficient in the vast majority of those cases [18]. For the insulin-producing beta-cell originating tumour insulinoma, sstr-2 is less frequently expressed (around 50%), as these tumours express more often somatostatin receptor subtype 5 as compared to other EPT. Thus, around 50% are not responsive to SSA and higher doses of octreotide acetate may be required for effective inhibition of insulin secretion in insulinoma patients.
6.4.3. Antiproliferative treatment

While the initial indication for the use of SSA was for control of symptoms related to hypersecretion of amines or peptides, recent literature has now suggested their use and effectiveness as an antiproliferative therapeutic agent in midgut NETs shown by the recent PROMID study from Germany. In this study, time to tumour progression (TTP) in patients receiving monthly intramuscular injections of 30 mg Sandostatin-LAR was more than doubled compared to patients receiving placebo i.m. saline injections (TTP 14.3 vs 6.0 months). It treatment regimen was equally effective in both functioning and non-functioning tumours, and was independent of Cg-A serum values. In this investigated cohort, patients were therapy-naïve; time from diagnosis to treatment was 4.3 months. Liver tumour load was <10% in more than 75% of the patients [2].

The CLARINET study is an ongoing placebo controlled trial using Lanreotide Autogel 120 mg in non-functioning entero-pancreatic NETs.

There are numerous retrospective and prospective uncontrolled studies investigating the antiproliferative effect of short-acting and long-acting octreotide and lanreotide. These studies provide evidence of partial remission in 0-8% and tumour growth arrest in 50-60% of the patients as best responses [16, 19]. The recent placebo controlled PROMID study suggests using SSA in midgut NETs, as it prolongs time to tumour progression even in limited disease. The NCCN guidelines and very recently the ENETS guidelines added octreotide as an antiproliferative treatment option [19]. The following table provides an overview of SSA indication for functional and non-functional NETs.
TABLE 6.1. CLINICAL USE OF SOMATOSTATIN RECEPTOR AGONISTS

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Symptoms</th>
<th>sstr2 Scintigraphy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal carcinoids</td>
<td>Flush, diarrhea, fatigue, R-sided heart disease, wheeze</td>
<td>Positive for primary NET and/or mets</td>
<td>Octreotide (sc or IV) for acute exacerbation; Octreotide LAR or Lanreotide AutogelΦ for chronic use</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Positive for primary NET and/or mets</td>
<td>Octreotide LAR or Lanreotide AG should be considered if CT/MRI show tumour progression or new lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Octreotide LAR may be considered for prevention of tumour progression upon diagnosis</td>
</tr>
<tr>
<td>Lung carcinoids*</td>
<td>Rarely flush, diarrhea from mediator secretion</td>
<td>Positive for primary NET and/or mets</td>
<td>Octreotide LAR or Lanreotide LAR or Lanreotide AutogelΦ for chronic use</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Negative</td>
<td>Octreotide LAR or Lanreotide AG should be considered along with other options when progression of tumour documented by CT/MRI</td>
</tr>
<tr>
<td>Gastrinoma*</td>
<td>Acid diarrhea, abdominal pain, esophagitis</td>
<td>Positive for primary NET and/or mets</td>
<td>Octreotide LAR or Lanreotide AutogelΦ in combination with PPIs</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Positive or negative mets</td>
<td>Octreotide LAR or Lanreotide AG may be considered along with other options when progression of tumour documented by CT/MRI</td>
</tr>
<tr>
<td>Insulinoma*</td>
<td>Hypoglycemia, Neuroglycopenia</td>
<td>Positive for primary NET and/or mets</td>
<td>Octreotide LAR or Lanreotide AutogelΦ in combination with anti-hyperglycemic drugs, e.g., diazoxide</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>Positive or negative mets</td>
<td>Cautious trial of Octreotide or Lanreotide if positive OctreoScan® as hypoglycemia may worsen</td>
</tr>
<tr>
<td>VIPoma*</td>
<td>High volume secretory diarrhea, hypokaliema</td>
<td>Positive for primary NET and/or mets</td>
<td>Octreotide s.c./i.v. for acute exacerbation, octreotide LAR or lanreotide AutogelΦ for chronic use</td>
</tr>
<tr>
<td></td>
<td>High volume secretory diarrhea</td>
<td>Positive for primary NET and/or mets</td>
<td>Higher doses Octreotide s.c./i.v. or Lanreotide AG Φ to antagonize intestinal secretion with concurrent steroids</td>
</tr>
<tr>
<td>PPoma (Pancreatic polypeptidoma)</td>
<td>Usually no symptoms</td>
<td>Almost always OctreoScan® positive</td>
<td>Octreotide or Lanreotide if CT/MRI show tumour progression or new lesions; other options to be considered</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Usually no symptoms</td>
<td>Almost always OctreoScan® positive</td>
<td>Octreotide or Lanreotide if CT/MRI show tumour progression or new lesions</td>
</tr>
</tbody>
</table>
Glucagonoma  | Skin rash (necrolytic migratory erythema), glossitis, diabetes, rarely diarrhea | Positive for primary NET and/or mets | Octreotide LAR or Lanreotide AG

**Pheochromocytoma, paraganglioma**  | Pallor, hypertension, perspiration | Positive for primary NET and/or mets | Octreotide LAR or Lanreotide AG combined with anti-hypertensive drugs

**Medullary thyroid carcinoma**  | No symptoms; may be associated with diarrhea | Positive for primary NET and/or mets | Octreotide or Lanreotide should be considered along with novel drugs if CT/MRI show tumour progression or new lesions

*Can be associated with MEN-1, **Can be associated with MEN2, Ψ VHL or SDHB, Φ Lanreotide Autogel not approved for NET in USA

### 6.4.4. Pharmacokinetics and application of somatostatin analogs

**Octreotide** somatostatin analogues (SSA) are available on the market both as subcutaneous and long acting repeatable (LAR) forms. The subcutaneous form is injected as an aqueous solution, 60-70% of the subcutaneously injected dose is absorbed resulting in a peak serum concentration following 30 minutes and a plateau is reached after 60 minutes. The plasma half-life is approximately 120 minutes but only 60 minutes if it is injected intravenously.

The long-acting repeatable form of octreotide is available in 10, 20, or 30mg concentrations as a polymer suspension. This suspension is absorbed at various rates over a period of 28 days. There is a large release into the circulations of octreotide acetate following the first 24 hours after the intramuscular injection, this is followed by a 7-8 day period where very little octreotide is released into circulation. The treatment regimen usually requires at least three monthly intra muscular injection intervals to achieve plasma saturation and a steady state condition level of serum octreotide. When using octreotide for patients with symptoms of diarrhea or flushing it is important to use a subcutaneous octreotide formulation for 8 days before the i.m. LAR injection and thereafter to continue with the s.c. octreotide acetate for an additional 8-10 days to assure a adequate “loading” serum level. We recommend a subcutaneous loading dose of 100-200mcg 3x daily both before and for 7-10 days following the i.m. injection. In addition, it is advisable to empirically initiate the s.c. form of octreotide at a dose of 100mcg 3x daily before putting patients on the LAR form this to ensure patient’s tolerability to the LAR form.

The pharmokinetics of **lanreotide**, which was available as a subcutaneous form in Europe, is similar to that of octreotide acetate. Short acting form of lanreotide is not available in Europe, currently only a lanreotide depot-form is available in Europe and in the United States. Both the subcutaneous and the Autogel forms have similar absorption rates (60-70%) similar to the absorption of octreotide acetate. The monthly lanreotide depot is injected into the deep subcutaneous tissue and does not require pre-reconstitution as does Sandostatin-LAR. It is important to remember that for both depot formulations blood and tissue saturation is attained only after three months of starting the LAR therapy form, this fact necessitates the use of the subcutaneous form during the initial treatment phase.
6.5. Side effects

The most frequent side effects are gastrointestinal comprising abdominal discomfort, nausea or diarrhea that are commonly transient. The risk of developing cholecystolithiasis and gall bladder "sludge" caused by chronic somatostatin analogue therapy is often precluded by performing a prophylactic cholecystectomy during the first surgical exploration to remove the primary gastrointestinal/pancreatic neuroendocrine tumour. Cholecystectomy may be required if long-term use of the somatostatin congeners is considered, especially when these are effective in controlling symptoms and partially controlling tumor proliferation. The mechanism of steatorrhea or fat malabsorption is caused by the secretory inhibition of postprandial exocrine pancreatic enzymes. The latter side effect can be well managed by prescribing pancreatic enzyme replacement (pancrease-lipase).

6.6. Interferon

Interferon -alpha (INF-α) has been used for treatment of patients with neuroendocrine tumours, especially with the carcinoid syndrome, for more than 25 years and, with somatostatin analogues. It is considered the main antisecretory drug used in the treatment of these tumours [19, 20]. Treatment with INF-α effectively reduces hypersecretion-induced symptoms in patients with the carcinoid syndrome similar to SSA. Its effect on symptom control is comparable to that of somatostatin analogs; however, it is not a standard treatment for carcinoid crisis.

In a large study of patients with malignant carcinoids and hepatic metastases, 70% of the patients experienced an improvement of flushing or diarrhea or both when INF-α 2b was used at a dose of 5 MU s.c. thrice weekly or natural INF-α daily. Biochemical response was obtained in 42% of these patients, and significant tumour shrinkage was achieved in 15%. Stabilization of tumour growth is considered an important response and was reported in 39% of the patients [21]. A biochemical and symptomatic response is reported in up to 50% of patients, whereas partial tumour size responses could be demonstrated in 10–15% [19, 22]. The duration of response was 12–36 months. Interferon is also effective in endocrine pancreatic tumours [22].

Side effects of INF-α are very common, limiting dose and treatment duration. Side effects include flu-like symptoms in over 90% of the patients, weight loss and fatigue. Major side effects include autoimmune reactions, depression and mental disturbances. Bone marrow toxicity is usually mild as is hepatotoxicity, which can be managed by dose adjustments.

Pegylated interferon (PEG IFN) can be considered an alternative treatment to the conventional regimen of INF-α thrice weekly, if the latter is not well tolerated [23]. PEG-IFN is at least equally effective as compared to the conventional regimen. Data are, however, limited and it is not officially registered for the treatment of NETs. Better tolerability of PEG-IFN-α in contrast to conventional IFN-α regimen has been demonstrated in patients with chronic myeloid leukemia and solid tumours, such as metastatic melanoma and renal cell carcinoma.

In neuroendocrine tumours, administration of PEG-IFN-α at dosages of 50-100 µg, once weekly, was associated with less frequent (24%) and shorter persisting acute flu-like symptoms than reported in the literature for non-pegylated IFN-α.
To assess hematological side effects, repeated white and red blood cell counting is recommended. Monitoring liver enzymes and TSH level is required at the beginning and during follow-up.

6.7. Concluding remarks on the use of SSA

In Europe the use of the SSA combined with IFN-α is the only approved therapy for treating symptomatic neuroendocrine tumours. SSA can be virtually used alongside all other therapeutic options discussed in this chapter. They are mandatory prior to any invasive intervention at the tumour site including surgery, local ablation or embolization and prior to general anaesthesia to prevent carcinoid crisis. Given the knowledge that between 87-92% of all neuroendocrine tumours express sstr-2, patients should always be offered this treatment option alongside other treatments, and in the framework of supportive care. Further more, recent results of the placebo-controlled study in small intestinal (midgut) NET highlights the tumour-growth inhibitory effect that has been suggested by several prior uncontrolled prospective and retrospective studies. The benefits of the commercially available SSA far outweigh their risks.

For instructions on the withdrawal of SSA medications prior to the delivery of PRRNT please refer to Section 7.5.1.

6.8. Chemotherapy

Systemic chemotherapy is effective in some patients, especially those with poorly differentiated neuroendocrine carcinoma (PDEC)/neuroendocrine carcinoma (G3) and progressive NET of the pancreas. In well differentiated midgut NET/ neuroendocrine tumours grades G1 or G2, however, response rates to chemotherapy are low (7-20%) and no survival advantage could be demonstrated [24, 25].

The standard treatment of neuroendocrine carcinoma (G3) is cisplatin and etoposide. Cisplatin inhibits DNA synthesis; etoposide is cytostatic drug arresting cells cycle in the S and G2 phases and inhibits mitosis. The response rate with this combination is 42-67%, but often of short duration (8-9 months) [24]. The combination of irinotecan and cisplatin [26] or FOLFOX chemotherapy (5-Fluorouracil or capecitabine and Oxaliplatin) may be an alternative treatment regimen [27]. However, the 2 years survival rate is less than 20% in neuroendocrine carcinoma grade G3.

PRRNT is rarely a treatment option in neuroendocrine carcinoma (G3) due to low expression of sstr, but it may be considered after failure of chemotherapy if sstr targeting is sufficiently high as determined by functional imaging using OctreoScan® or ⁶⁸Ga-DOTATOC PET-CT.

Treatment options of malignant, inoperable endocrine pancreatic neuro-tumours include somatostatin analogs, systemic chemotherapy, and PRRNT. If the tumour is functional, the use of somatostatin analogs is considered first-line therapy.

Streptozotocin (Zanosar; STZ)-based systemic chemotherapy is considered a standard therapy in progressive pancreatic neuroendocrine tumours with low or moderate proliferative capacity. Streptozotocin is an alkylating nitrosourea compound and is used in combination with 5-Fluorouracil (5-FU) and/or doxorubicin. 5-FU inhibits thymidilate synthetase and leads to cellular thymidine depletion and cell death. Doxorubicin binds to the DNA and inhibits DNA and RNA synthesis. Combinations of STZ and 5-FU and/or doxorubicin lead to partial
remission rates of 35-40% [28-30]. In earlier trials where clinical criteria for response assessment were used, the reported response rates were higher (up to 69%) [30]. Overall response duration is about 1-2 years. Streptozotocin is, however, not widely available, but is approved both in the U.S., since 1976 by the Food and Drug Administration, and in Switzerland. In highly aggressive neuroendocrine carcinomas of the pancreas (proliferation >20%) platin-based chemotherapy is recommended by ENETS guidelines.

Recent phase II studies indicate efficacy of temozolomide-based chemotherapy, either with antiangiogenic drugs or capecitabine. However, the number of patients included in these trials is low. These initial results reporting response rates of up to 70% do warrant further investigations in the framework of phase III trials for confirmation [31-33].

Standards of care for the use of chemotherapy have been defined by ENETS [34].

6.9. Molecular targeted therapies

6.9.1. Introduction

Cell proliferation and differentiation are regulated by hormones, growth factors, and cytokines. These molecules interact with cellular receptors and via intracellular signaling pathways with the nucleus of the cell. In cancer cells key components of these pathways may be altered, overexpressed, or mutated. Dysregulation of cell signaling and inhibition of cell proliferation and metastasis are the consequences. The components of these signaling pathways represent potential selective targets for new anticancer therapies. These targets include ligands, cell membrane receptors, intracellular second messengers, and transcription factors.

In recent years, molecular targeted therapies have been used in clinical trials of neuroendocrine tumours given the expression of various growth factors or receptors and secretion of growth factors. This approach includes neutralization of ligands to growth factor receptors, e.g. Bevacizumab, a humanized monoclonal antibody targeting circulating vascular endothelial growth factor (VEGF), and inhibition of growth factor receptors by tyrosine kinase inhibitors, small molecules that inhibit receptor phosphorylation, e.g. gefitinib. Examples for the multispecific inhibition of signaling of cytoplasmic secondary messengers are imatinib, an inhibitor of the kinase activity of bcr-abl, c-kit and platelet derived growth factor receptor (PDGFR) and sunitinib, an inhibitor of RET, c-kit, PDGFR and VEGFR. In colon cancer and non-small cell lung cancer (NSCLC) the application of antibodies against circulating growth factors or growth factor receptors represents established therapy.

Novel therapies may be summarized as angiogenesis inhibitors, single or multiple tyrosine kinase inhibitors (small molecules) and somatostatin receptor targeted therapies, like the novel SSA analogue pasireotide (SOM230), a cyclohexapeptide that binds to sstr subtypes 1, 2, 3, and 5, it . It displays a 30-40 fold higher affinity to the sstr1 and sstr5 than Sandostatin.

6.9.2. Anti-angiogenic pharmaceuticals

Angiogenesis inhibitors are currently undergoing clinical evaluation in combination with other drugs for treating gastronteropancreatic NET. The most developed drugs in this field are Bevacizumab and Sunitinib.
In a phase II trial in 44 patients with advanced carcinoid tumours, the first clinical evidence was reported that Bevacizumab in combination with octreotide LAR leads to partial tumour remission in 18% [35] and is superior to a treatment with octreotide and pegylated interferon-alpha. Stable disease was observed in 77% of patients on bevacizumab; however, disease status at study entry was known only in a subgroup of patients. A large phase III study (SWOG S0518; www.clinicaltrials.gov) is currently recruiting patients to confirm these results. The treatment was associated with a significant decrease in tumour blood flow. Toxicity profile was favourable with hypertension as the most frequent adverse event.

In a phase II study, in combination with temozolomide, a response rate of 24% was achieved [36]. Bevacizumab is currently tested in combination with other drugs such as cytostatics, e.g. with oxaliplatin-based chemotherapy (see NCI Homepage; ClinicalTrials.gov database).

Sorafenib was investigated in a phase II trial with 93 patients. The overall response rate was 10% in both carcinoid and islet cell tumours. Minor responses were observed in both patient groups [37]. Several drug combinations are under investigation with either everolimus, bevacizumab, or metronomic chemotherapy.

6.9.2.1. **Sunitinib malate**

Is an oral multi-targeted tyrosine kinase inhibitor of VEGFR, PDGFR, c-kit, RET and FLT-3, with antiangiogenic and antitumour activities. Sunitinib was first studied in a phase II study in 107 patients (41 carcinoid tumours, 66 endocrine pancreatic tumours). The response rate was 16.7% in pancreatic endocrine tumours, and 2.4% in carcinoid tumours. The rate of Stable disease was 68 and 83% respectively [38]. A recent international phase III study of sunitinib versus placebo in patients with progressive well-differentiated endocrine pancreatic tumours was stopped early; however, only 171 out of 340 planned patients were investigated. The primary endpoint of the study was progression free survival (PFS). PFS was superior in the sunitinib arm with 11.1 months compared to 5.5 months in the placebo arm [39]. Objective remission rate was less than 10%. Most frequent side effects included diarrhea (59%), nausea (45%), vomiting (33%), asthenia (33%) and fatigue (32%). Adverse events were rarely grade 3 or 4 and included hypertension (10%) and neutropenia (12%) as the most frequent serious side effects [38]. The drug has recently been approved by the U.S. FDA and the European Commission for the treatment of advanced and progressive well-differentiated pancreatic NET. Sutent is also approved for this indication in the Philippines, Switzerland, Colombia and Korea.

6.9.3. **mTOR pathway targeting molecules**

The mammalian target of rapamycin (mTOR) inhibitor is structurally related to rapamycin. The protein kinase mTOR exerts a central control function involving multiple signaling pathways in response to growth factors and intracellular signaling by nutrients. The mTOR is involved in the regulation of growth-related cellular functions; the best known function is the regulation of translation initiation. Inhibiting mTOR pathway may reduce cell growth and proliferation and impair the metastatic potential of tumour cells. It also acts on the endothelial cells.

RAD001 (5 or 10 mg p.o./day) and the long acting somatostatin analogue octreotide LAR (30 mg q 28 days) were given to 60 patients with NET (30 with carcinoid tumours, 30 with PNET). Tumour response rate was 22% (with a higher response rate in islet cell tumours
compared to carcinoid tumours, 17\% vs. 27\% respectively). Stable disease was reported in 70\%; however, tumour status at study entry was not known in all patients [40].

A large clinical ongoing trial was initiated to further evaluate the value of Everolimus in carcinoid and endocrine pancreatic tumours. More than 1000 patients with neuroendocrine tumours have been included in clinical different trials with Everolimus, e.g. RADIANT-1, RADIANT-2, RADIANT-3 trials, RAMSETE trial.

Antitumour activity has been confirmed with Everolimus in patients with progressive metastatic pancreatic NET after failure of at least one line of cytotoxic chemotherapy in the RADIANT-1 trial. 160 patients were included in two Strata +/- Octreotide. The partial remission rate was low with 9.6 and 4.4\% respectively. The rate of disease stabilizations was, however, high with 67.8\% and 80\% respectively. The PFS were 9.7 and 16.7 months respectively [41]. Efficacy of Everolimus has been confirmed in a large international placebo-controlled trial including 410 patients with progressive pancreatic NET (RADIANT-3) [42]. The primary endpoint of this study was progression-free survival (PFS). Best supportive care including use of SSA was allowed in both study arms. Everolimus significantly reduced the risk of disease progression and lead to a prolongation of PFS compared to placebo by 6.4 months (11 months with Everolimus vs 4.6 months with placebo). Objective tumour response was low, confirmed partial remission was observed in 4.8\% of the patients. Disease control rate (PR+SD) was, however, high with 77.7\% with Everolimus compared to 52.7\% with placebo + best supportive care. At 18 months among the patients treated with everolimus there were still 34.2\% progression-free survivors compared to 8.9\% in the placebo arm. Most frequent side effects included stomatitis/apthous stomatitis (64\%), rash (49\%), and diarrhea (34\%), and fatigue (31\%). Side effects that merit special consideration are infections (23\%) and pulmonary events (lung infiltrates, interstitial pneumonitis) (17\%). Side effects were rarely grade 3 or 4; the most frequently reported include stomatitis (7\%), anemia (6\%), and hyperglycemia (5\%). Patients with severe or intolerable adverse reactions may require temporary dose reductions to 5 mg per day or dose interruption [42].

In May 2011 the U.S. FDA approved everolimus (Afinitor®), made by Novartis Pharmaceuticals Corporation, for the treatment of progressive neuroendocrine tumours of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease.

Everolimus was also investigated in a phase III trial with concomittant stable dose of Octreotide compared to Placebo (RADIANT-2) in patients with symptoms associated with the Carcinoid syndrome. This study is the largest randomized prospective study that has ever been done in this type of NE tumour. The primary endpoint was PFS by central adjudicated review. With oral daily everolimus (10 mg/d) + octreotide LAR 30 mg once every 4 weeks, PFS was 16.4 months compared to placebo + octreotide LAR 30 mg every 4 weeks with 11.3 months (HR 0.77). The primary endpoint was, however, narrowly missed (p-value 0.026; pre-specified p value 0.0246). Local radiological review is consistent with the central analysis leading to a similar risk reduction (Hazard ratio 0.78) [43]. The effectiveness of everolimus in the treatment of patients with carcinoid tumours was considered to be not established by the U.S. FDA. Further trials with everolimus in comparative designs and in combination with other drugs in different types of NET are currently ongoing.

In summary, the antitumoural activity of novel targeted drugs is moderate with low partial remission rates, but high rate of disease stabilization in phase II and III trials. The drugs with the highest evidence of efficacy are Sunitinib and Everolimus. Both drugs lead to
prolongation of the PFS in advanced pancreatic NET. For Everolimus there is evidence for the efficacy in treating NETs of other than pancreas that are associated with the carcinoid syndrome.

6.10. Loco-regional approaches

Neuroendocrine tumours often metastasize into the liver, which represents a poor prognostic factor. Loco-regional approaches or local ablative therapies target predominantly liver metastases with the goal to achieve local tumour control to improve functional syndromes. To this end, different techniques are applied which may depend on individual factors (morphology, size, vascularization, distribution of lesions), functional activity of neuroendocrine tumours, local expertise and local availability. As such, most published results are derived from retrospective analysis in single centers [13].

Different technical approaches are utilized for local ablative and loco-regional therapies, to either achieve direct tumour destruction or reduction of the vascular flow to the liver lesions (embolization).

Older techniques, such as instillation of cytotoxic agents like ethanol (PEI) or acetic acid (PAI) are difficult to control and have limited value as local ablative therapy for neuroendocrine tumours in the liver as well as cryoablation [13, 44]. These are replaced by other techniques.

Direct destruction of the tumour by radiofrequency ablation (RFA) or laser-induced interstitial thermoablation (LITT) is advantageous if tumour load and the number and size of lesions are limited. These treatment options are feasible in combination with debulking surgery. In these conditions, portal vein embolization may help to combine surgery and local ablative therapies with curative intent. Radiofrequency ablation (RFA) is effective for relieving symptoms and achieving local tumour control. RFA is the preferred method of local ablative therapy in most centers and may be very well combined with surgery. In a recent series on 16 patients treated with RFA and surgery, an overall 5-year survival of 90% was reported with 48% being disease-free [45]. For RFA used as monotherapy, patients with specific symptoms had significant or complete relief of symptoms in 70% of the cases. Duration of symptom control was 11 +/- 2.3 months [46]. Morbidity of RFA has to be considered as well as the need of repeated interventions for patients with neuroendocrine liver metastases.

Targeting arterial perfusion of neuroendocrine tumours in the liver include transcatheter arterial embolization (TAE), transcatheter arterial chemoembolization (TACE) and selective internal radiotherapy (SIRT). To occlude vessels of neuroendocrine tumours, oil-based contrast agents such as lipiodol or beads may be used, both of which may be loaded with cytotoxic agents such as doxorubicin. Local embolization techniques are especially useful when treating patients with functionally active liver metastases. With TACE symptomatic response rates of 60-95%, biochemical response rates of 50-90% and radiological response of 33-80% were achieved [13, 44, 47, 48]. Response duration is between 18 and 24 months. Similar response rates are achieved with TAE alone [44]. In general, the procedure may require repeated interventions.

Coupling beads for embolization with the beta-emitter 90-Yttrium requires extensive preparation of arterial liver vessels to prevent retrograde perfusion to prevent radiation damage to neighboring internal organs. In addition, shunting of liver vessels to the lung has to be estimated before therapy. Response rates vary between individual centers [49, 50],
prospective studies are, however, lacking. In one prospective study including 34 patients the objective response rate was 50% [49].

In the lack of comparative studies of different techniques used for local ablative and loco-regional therapies, the choice of the technique will highly depend on the physicians’ experience in the different treatment centers and on individual criteria such as number, size, vascularization and distribution of the lesions.

In summary, for singular or few liver lesions local resection or RFA and/or LITT can be recommended, while in multinodular diseases with higher tumour load, TACE or TAE is the method of choice. All the therapies described above are not without risk and should be performed in highly experienced centers. Prospective and comparative studies are warranted.

6.11. Supportive and palliative care

6.11.1. Nutrition

Cachexia is perhaps the leading cause of death in cancer patients [51]; this state of inflammation, anorexia and weight loss is accompanied by an outpouring of cytokines, neuroendocrine hormones, and catabolic factors that result in a failure of nutrition to engender anabolism [52].

Weight loss is a poor prognostic sign in many types of cancers, and is associated with decrease in both the length and quality of life [52]. This is especially so in neuroendocrine tumours, because diarrhea is a common side effect in NET that secrete serotonin, substance P, or vasoactive intestinal peptide [53]; further, serotonin may induce a cachetic state in addition to the diarrhea [54]. An example of the importance of adequate nutrition in the care of patients with NET is the observation that patients treated with PRRNT experienced an average 20 month survival if diarrhea was controlled, compared to 11 months for those with continued diarrhea [55].

Nutrition is therefore an essential component of care when delivering PRRNT. The goal must be to control diarrhea and inflammation, promote weight gain and, most importantly, induce an anabolic state of tissue repair [52]. Nutritional questionnaires filled out by patients appear to correlate well with measurements of plasma levels of tocopherols, carotenes, trans-fat, omega-3, lipo-proteins and cholesterol [56].

Teaching points:

1. Weight loss before and during cancer treatment is associated with decreased quality of life and decreased survival.

2. The goal in nutritional supplementation is to decrease the inflammatory state and associated cachexia, improve appetite, to induce an anabolic state leading to increased muscle mass and physical activity.

3. Analysis of nutritional questionnaires completed by patients appears to be comparable to measurement of plasma levels of nutrients in determining metabolic state during chemotherapy.
6.11.2. Pain control

The quality and severity of pain should be taken seriously, assessed and documented. If possible, the underlying nature causing pain should be treated, for instance, obstruction in the gastrointestinal tract. Treatment of pain in patients with neuroendocrine tumours follows the general principles in adult and pediatric oncology and depends on local availability and expertise. Thus, it is advisable to follow local and current guidelines [57]. Effective treatment of neuroendocrine tumours may alleviate pain [55]. Pancreatic neuroendocrine tumours infiltrating the retroperitoneum may be treated by nerve blockade of the celiac nerve plexus [58]. Treatment of painful bone metastases is compiled below.

6.11.3. Evaluation and treatment of bone metastases

Bone metastases are reported in ~15% of patients with neuroendocrine tumours. Due to incomplete staging the frequency of bone metastases from NET is probably underestimated. With the use of more sensitive imaging techniques the detection of bone metastases will probably increase. According to a recent study, Ga-68 DOTATOC PET seems a reliable, novel method for the early detection of bone metastases in patients with neuroendocrine tumours [59]. Exact assessment of bone metastases is essential, because bone metastases may induce pain, neural damage or pathological fractures (although the latter are rare in neuroendocrine tumours due to the osteoblastic nature of the majority of bone metastases). Bone metastases of neuroendocrine tumours are often invisible on plain X-rays but may be picked up by CT or MRI scanning. The detection of asymptomatic bone metastases is further increased by the use of somatostatin receptor scintigraphy. However, Ga-68 based somatostatin receptor PET/CT is more sensitive than scintigraphy or CT [60]. 1F-18 fluoride PET/CT may be also used to detect bone metastases of neuroendocrine tumours with high sensitivity [61].

Treatment of bone metastases of neuroendocrine tumours follows the same principles as in other cancers [62] and includes application of bisphosphonates as a basis therapy. Since osteonecrosis may occur under this treatment, assessment of the dental status is required. In case of vitamin D deficiency, supplementation therapy is mandated. Painful bone metastases respond to external beam radiation, which may be also indicated to prevent pathological fractures. Other treatment options include PRRNT as for other metastases, or Samarium-153 EDTMP therapy [63].

6.11.4. Family counselling and patient’s support

Most neuroendocrine tumours are sporadic, but a minority may have a hereditary background. According to frequency, hereditary tumour syndromes with development of GEP NETs are (a) multiple endocrine neoplasia (MEN) syndrome, (b) neurofibromatosis type 1, (c) von Hippel-Lindau syndrome, (d) tuberous sclerosis complex [64-66]. All of these diseases are based on autosomal-dominant inheritance involving tumour-suppressor genes.

Loss of heterocigosity (generally chromosomal loss of the second, non-mutated allele) is the basis for tumour occurrence. Since these patients may present with multiple neuroendocrine tumours or disorders, suspicion should always be high and clinical presentation should be known. In addition, patients may present in their childbearing years and have offspring which may be affected with potentially preventable diseases such as medullary thyroid cancer.
The most frequent syndrome is MEN 1 caused by heterzygous mutations in tumour suppressor menin gene. Patients with MEN 1 present initially with hyperparathyroidism and tumours of the adenohypophysis. Neuroendocrine tumours of the pancreas occur in patients with MEN 1 with almost 100% penetration with increasing age. Often this involves so-called microadenomas (size <5 mm). If neuroendocrine tumours are functionally active, most often hyperinsulinemic hypoglycemia is present caused by insulinoma. Patients with MEN 1 may frequently develop Zollinger Ellison syndrome caused by gastrinomas, which are often duodenal, multiple and already metastasized at a size of less than 2 mm. Detection of the primary in the presence of large lymph node metastases poses a particular interdisciplinary challenge considering the tiny size of these tumours. In parallel, patients with MEN 1 and duodenal gastrinomas develop tumours of the ECL cells of the stomach. Hypergastrinemia as trophic factor, along with the MEN 1 germline mutation, present in all somatic cells, is the cause for the development of these ECL cell tumours. Multiple endocrine neoplasia like syndrome was detected recently. It is caused by mutations in the p27 gene and the phenotype resembles MEN 1 [64, 66].

Mutations in the proto-oncogen RET cause multiple endocrine neoplasia syndrome 2 with its hallmark medullary thyroid cancer, which is associated with pheocheomocytomas (MEN 2A) and also by enteral neural hyperplasia visible as neuromas on the tongue (MEN 2B).

Von Hippel-Lindau disease presents with pheochromocytoma, kidney tumours and pancreatic neuroendocrine tumours, which may be multiple. Patients with Carney complex, which is caused by mutations in protein kinase A regulatory subunit type 1-alpha (PRKAR1A) present with pigmented skin disorders, cardiac myxomas and endocrine tumours (Horvath and Stratakis 2009).

It is to be presumed that a far larger number of GEP NETs as previously assumed have a hereditary background. It is known from individual population-based studies that some of the GEP NETs appear clustered in families without being able to identify specific factors for this. In addition, it is known that some of the GEP NETs are multiple like serotonin-producing NETs of the ileum.

In patients suspected to harbour germline mutations, genetic counseling should precede genetic testing.

Patient advocacy groups are active in many countries worldwide. These organisations are important due to their contribution to the awareness and understanding of neuroendocrine tumours, not only for patients but also for physicians treating patients with this rare disease. Patient advocacy groups distribute information to patients and in some instances also support research and clinical trials. Ideally, patient advocacy groups are involved in the evaluation of new treatments at an early stage.
REFERENCES


7. PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRNT)

7.1. Introduction

7.1.1. Historical development

Capitalizing on the favourable pharmacokinetic and the cellular internalization of octreotide this molecule labelled with $^{111}$In-DTPA a potent tool was available for the visualization and clinical diagnosis of tissue expressing somatostatin receptors. This radiopharmaceutical was established in clinical routine introduced as the $^{111}$In-labelled octreotide ($^{111}$In-pentetreotide). In 1994 it was approved by the FDA as a scintigraphic agent for patients with neuroendocrine tumours (NETs). Once octreotide was radiolabelled for diagnostic imaging in order to localize tumour lesions over-expressing somatostatin receptors [1], the next logical step was to develop a peptide receptor radionuclide therapy (PRRNT). The theoretical basis of PRRNT is to convey radioactivity inside the tumour cell, owing to the internalization of the somatostatin receptor and radiolabelled analogue complex. The first attempts to perform PRRNT with radiolabelled octreotide began in the 1990s in a multicentre trial using high activities of the diagnostic compound $^{111}$In-octreotide. The results obtained, in terms of clinical benefit and overall responses, are due to the Auger and conversion electrons emitted by Indium-111, decaying in close proximity to the cell nucleus, once that peptide/receptor complex has been internalized. Despite these premises, partial remissions were exceptional [2]. Higher-energy and longer-range emitters, such as pure $\beta$ emitter Yttrium-90 ($E_{\beta_{\max}}$ 2.27 MeV, $R_{\beta_{\max}}$ 11 mm, $T_{1/2}$ 64 hrs), seemed more suitable for therapeutic purposes. Therefore, a new analogue, Tyr$^3$-octreotide, with a similar pattern of affinity for somatostatin receptors, was developed for its high hydrophilicity, simple labelling with $^{111}$In and $^{90}$Y, and tight binding to the macrocyclic chelator DOTA (1,4,7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid), to form $^{90}$Y-[DOTA]$^0$-Tyr$^3$-octreotide or $^{90}$Y-DOTATOC [3]. Recently, a newer analogue, named octreotate (Tyr$^3$,Thr$^8$-octreotide) with 6- to 9-fold higher affinity for sstr2 was synthesized. The chelated analogue [DOTA]$^0$-Tyr$^3$-octreotate or DOTATATE can be labelled with the $\beta$-$\gamma$ emitter Lutetium-177 ($E_{\beta_{\max}}$ 0.49 MeV, $R_{\beta_{\max}}$ 2 mm, $T_{1/2}$ 6.7 days) and has been experimented in clinical studies since the beginning of new century.

Nowadays, tumour candidates for PRRNT with radiolabelled somatostatin analogues are basically sstr2-expressing NETs, mainly of the gastroenteropancreatic and bronchial tract, but also pheochromocytomas, paragangliomas, medullary thyroid carcinomas, and, at least theoretically, any other tumour histological type known and documented as overexpressing sstr2.

PRRNT efficacy crucially depends on the radioactive concentration at the tumour site. In this regard, the most important influencing factors are the receptor affinity of the radipeptide and the receptor density of the tumour [4].

7.1.2. Rationale

Neuroendocrine cells are typically regulated by a number of hormones, exerting their action via specific receptors on the membrane surface. These receptors are transmembrane-domain G-protein–coupled receptors. The most exploited and known ligand-receptor system in clinical practice is the somatostatin. The rationale for the peptide receptor-targeted therapy is 1. the presence of a high density of somatostatin receptors expressed on the cell surface of
NETs, and 2. the fact that following the binding to the somatostating tagged radiopharmaceutical, the complex receptor-SSA is internalized by the cell. The sstr subtype 2 is the one most frequently expressed on NETs. As previously mentioned, in fact, somatostatin analogues, such as octreotide and lanreotide, are presently a mainstay in the treatment of tumour hypersecretion and of primary and metastatic lesion growth.

### 7.1.3. Peptide affinity and pharmacokinetics

The various octreotide derivatives available possess variable affinity profiles for sst2, sst3 and sst5. Peptides, such as DOTATOC and even more DOTATATE and DOTANOC possess a high affinity for sst2, the most widely expressed receptor in NETs (11, 1.5 and 3.3 IC50 nM, respectively; see Table 7.1, [5].

#### TABLE 7.1. AFFINITY PROFILES (IC50) OF A SERIES OF SOMATOSTATIN ANALOGUES TO THE FIVE SUBTYPES OF HUMAN SOMATOSTATIN RECEPTORS (STTR 1-5), ADAPTED WITH PERMISSION FROM [5].

<table>
<thead>
<tr>
<th>Peptides</th>
<th>hsstr 1</th>
<th>hsstr 2</th>
<th>hsstr 3</th>
<th>hsstr 4</th>
<th>hsstr 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS-28</td>
<td>5.2±0.3</td>
<td>2.7±0.3</td>
<td>7.7±0.9</td>
<td>5.6±0.4</td>
<td>4.0±0.3</td>
</tr>
<tr>
<td>Octreotide</td>
<td>&gt;10,000</td>
<td>2.0±0.7</td>
<td>187±55</td>
<td>&gt;1,000</td>
<td>22±6</td>
</tr>
<tr>
<td>CH288</td>
<td>23±2</td>
<td>&gt;10,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>DTPA-octreotide</td>
<td>&gt;10,000</td>
<td>12±2</td>
<td>376±84</td>
<td>&gt;1,000</td>
<td>299±50</td>
</tr>
<tr>
<td>In-DTPA-octreotide</td>
<td>&gt;10,000</td>
<td>22±3.6</td>
<td>182±13</td>
<td>&gt;1,000</td>
<td>237±52</td>
</tr>
<tr>
<td>DOTA-TOC</td>
<td>&gt;10,000</td>
<td>14±2.6</td>
<td>880±324</td>
<td>&gt;1,000</td>
<td>393±84</td>
</tr>
<tr>
<td>Y-DOTA-TOC</td>
<td>&gt;10,000</td>
<td>11±1.7</td>
<td>389±135</td>
<td>&gt;10,000</td>
<td>114±29</td>
</tr>
<tr>
<td>DOTA-LAN</td>
<td>&gt;10,000</td>
<td>26±3.4</td>
<td>771±229</td>
<td>&gt;10,000</td>
<td>73±12</td>
</tr>
<tr>
<td>Y-DOTA-LAN</td>
<td>&gt;10,000</td>
<td>23±5</td>
<td>290±105</td>
<td>&gt;10,000</td>
<td>16±3.4</td>
</tr>
<tr>
<td>DOTA-VAP</td>
<td>&gt;10,000</td>
<td>29±7</td>
<td>419±104</td>
<td>743±190</td>
<td>80±19</td>
</tr>
<tr>
<td>Y-DOTA-VAP</td>
<td>&gt;10,000</td>
<td>12±2</td>
<td>102±25</td>
<td>778±225</td>
<td>20±2.3</td>
</tr>
<tr>
<td>DOTA-OC</td>
<td>&gt;10,000</td>
<td>14±3</td>
<td>279</td>
<td>&gt;1,000</td>
<td>103±39</td>
</tr>
<tr>
<td>Y-DOTA-OC</td>
<td>&gt;10,000</td>
<td>20±2</td>
<td>27±8</td>
<td>&gt;10,000</td>
<td>57±22</td>
</tr>
<tr>
<td>Ga-DOTA-TOC</td>
<td>&gt;10,000</td>
<td>2.5±0.5</td>
<td>613±140</td>
<td>&gt;1,000</td>
<td>73±21</td>
</tr>
<tr>
<td>Ga-DOTA-OC</td>
<td>&gt;10,000</td>
<td>7.3±1.9</td>
<td>120±45</td>
<td>&gt;1,000</td>
<td>60±14</td>
</tr>
<tr>
<td>DTPA-[Tyr]-octreotate</td>
<td>&gt;10,000</td>
<td>3.9±1</td>
<td>&gt;10,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>In-DTPA-[Tyr]-octreotate</td>
<td>&gt;10,000</td>
<td>1.3±0.2</td>
<td>&gt;10,000</td>
<td>433±16</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>DOTANOC-111In</td>
<td>&gt;10,000</td>
<td>1.5±0.4</td>
<td>&gt;1,000</td>
<td>453±176</td>
<td>547±160</td>
</tr>
<tr>
<td>DOTANOC-111In</td>
<td>&gt;10,000</td>
<td>1.6±0.4</td>
<td>&gt;1,000</td>
<td>523±239</td>
<td>187±50</td>
</tr>
<tr>
<td>Ga-DOTA-[Tyr]-octreotate</td>
<td>&gt;10,000</td>
<td>0.2±0.04</td>
<td>&gt;1,000</td>
<td>300±140</td>
<td>377±18</td>
</tr>
</tbody>
</table>

The receptor density on tumour versus normal organs must be also considered. The higher is the density, the greater the amount of radiopeptide that can be delivered to interior of the tumour cells. In clinical practice, the density is evaluated by means of receptor scintigraphy, according to a visual scale, named the “Rotterdam scale” (Figure 7.1), where tumours may have an uptake on planar images lower than the normal liver tissue uptake (grade 1), equal to the one of the normal liver (grade 2), higher than that (grade 3) or higher than the one of kidneys and spleen, the “hottest” organs at 111In-octreotide scintigraphy (grade 4). Tumour
remission, in fact, is positively correlated with a high uptake at receptor scintigraphy [6, 7]. Usually tumours with grade 2 to 4 are candidates to PRRNT.

The pharmakokinetics behaviour of these molecules is very favourable, with a rapid plasma clearance and renal excretion, which results in a low total body irradiation.

PRRNT is still an investigational treatment and its implementation must comply with national legislation and local requirements, as well as with ethical principles regarding human studies.

FIG. 7.1. Intensity of tumour uptake as determined by $^{111}$In-Pentetreotide planar images. Panel (a) depicts tumour uptake in the left thorax lower than the normal liver tissue uptake (grade 1). Panel (b) shows several abnormal foci in the lower abdomen having equal uptake as to normal liver tissue (grade 2). Panel (c) depicts an upper mid-abdominal (pancreatic?) focus of abnormal activity higher than normal liver uptake (grade 3). Panel (d) depicts multiple foci of uptake in the liver and upper abdomen with a higher intensity than the kidneys and spleen (grade 4). Scintigraphic images are courtesy of Dr. J. Mueller-Brand.
FIG. 7.2. Whole body In-111 Octreotide scan acquired 6 hours p.i. in a 56-year-old patient with multiple liver metastatic lesions and a large mesenteric tumour mass showing variable degrees of tracer uptake indicated by black arrows. The Roman numerals indicate the level of uptake according to the Rotterdam scale (I-IV). Grey arrows point to the left and right kidneys. Whole body images show the biodistribution of the tracer beyond the gastro-intestinal tract. Note the intense physiological uptake of the tracer in the spleen appreciated on the posterior whole body view. Scintigraphic images are courtesy of Dr. J. Mueller-Brand.
7.1.4. **Tumours suitable for PRRNT**

Candidates include all tumours strongly expressing sst2 receptors, such as gastroenteropancreatic and lung NETs. In addition, pheochromocytomas, paragangliomas, meningiomas [8], medullary thyroid carcinomas [9, 10], de-differentiated thyroid cancer [11-13], and in theory any other tumour documented to overexpress sst2, can be a candidate for PRRNT.

7.1.5. **Outcome: response, survival and toxicity**

7.1.5.1. **Response**

The evaluation of response to PRRNT includes the assessment of functional and morphological responses, as well as the biochemical and symptomatic response, including the assessment of quality of life. The response is assessed by morphologic and functional imaging techniques. Please consider that post-therapeutic $^{177}$Lu-DOTATATE scans provide valuable information on the intensity of uptake and localization of the tracer and thus can be used to assess the response to the prior therapy cycles.

The timeline to assess the response may vary according to clinical needs (aggressiveness and extent of disease). Usually the first follow-up is recommended after 3 months, and the following controls should be performed after 3-6 months (see Figure 7.1.) The reader is also referred to the ENETS guidelines for a more detailed illustration of the standards of care in NET follow-up and documentation [14].

PRRNT with somatostatin analogues $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE has been explored in NETs for more than a decade. Present knowledge and clinical studies indicate that it is possible to deliver high absorbed doses to tumours expressing sst2 receptors, with partial and complete objective responses in up to 30% of patients.

The best objective responses have been reported in GEP NETs (with partial responses ranging from 9 to 29% and complete remission from 2 to 6%), as well as similar values in thorax (lung) NETs and neuroectodermic tumours (pheochromocytomas, paragangliomas). Less favourable results have been reported for thymic NETs, medullary thyroid carcinoma and de-differentiated thyroid carcinomas. Encouraging results have been reported also for SSR-positive tumours, such as meningiomas, medulloblastomas, astrocytomas [7-11, 15-17].

Figures 7.3. and 7.4. provide examples of two cases, the first showing a minor response Figure 7.1. while the second case demonstrates a partial response, as assessed by morphological imaging.
FIG. 7.3. Example of a minor response. Serial planar scintigraphic images of the abdomen (anterior and posterior views) using $^{111}$In-Octreotide, prior to the first and after the second and the third treatment cycles. Note marked decrease in the intensity, extension and number of metastastic lesions showing tracer uptake in the liver and in a large lymphatic metastases at the mesenteric root. MR-images of the abdomen prior to and 3 months after the last treatment cycle showing size reduction by about $20\%$ of major liver and mesenteric lesions, from $2\text{ cm}$ and $2.9\text{ cm}$, respectively (left panel) to $1.7$ and $2.4\text{ cm}$ in diameter (right panel) following the last cycle. Scintigraphic and CT images are courtesy of Dr. A. Belfer.
FIG. 7.4. Example of a partial response. Serial planar scintigraphic images of the abdomen (anterior and posterior views) using $^{111}$In-Octreotide, prior to the first and after the second, third and fourth therapy cycles (Y-90 DOTATOC), showing marked decrease in the intensity, extension and number of abnormal uptake in liver metastases. Note the presence of a horseshoe kidney well appreciated on the anterior planar views. T-2 weighted MR-images of the abdomen prior to and 3 months after the last treatment cycle show significant morphological response of all initially detected liver lesions.

Scintigraphic and CT images are courtesy of Dr. A. Belfer.
FIG. 7.5. Example of a partial response in a 38-year-old female with an inoperable pancreatic neuroendocrine tumour. Histology showed a highly differentiated NET (Ki-67 staining = 8%) and positive serum tumour markers of Cg-A and NSE. Serial 3D PET whole body studies presented as Maximum Intensity Projection (MIP) acquired using Ga-68 DOTATOC, corresponding CT (second row) and overlay of PET and CT (lower row). Baseline PET-CT study (column A) shows large tumour masses in the mid-upper abdomen with SUV max of 29.4. Patient underwent first cycle of PRRNT using 6 GBq (160mCi) Y-90 DOTATOC. Four months later PET-CT images show a moderate response of the tumour with a drop of SUV max to 24.4. A second PRRNT cycle was prescribed using 4.5 GBq (120mCi) Y-90 DOTATOC (column B). Column C presents PET-CT images 5 months following the second treatment cycle and a remarkable tumour response with a drop of SUV max to 12.5 alongside with marked tumour decline on CT. The patient was rendered operable and underwent a successful Whiple’s surgery (see FIG 7.6). PET-CT images are courtesy of Dr. R. P. Baum.
FIG. 7.6. A 38-year-old female presenting with an inoperable pancreatic neuroendocrine tumour who was rendered operable after undergoing two cycles of PRRNT using Y-90 DOTATOC (see also FIG. 7.5). Surgical specimen of the duodenum, head of the pancreas and a largely necrotic tumour mass by histology (left panel). Post-operative whole body PET-CT MIP image acquired after injecting 220 MBq of Ga-68 DOTATOC showing no evidence of residual cancer tissue. Images are courtesy of Dr. R. P. Baum.
7.1.5.2. **Survival**

Survival analyses indicate that patients having high somatostin receptor expression at study entry, undergoing treatment with $^{177}$Lu-DOTATATE or $^{90}$Y-DOTATOC, have significantly higher objective responses, translating in a significantly longer survival [7, 18, 19]. Additionally, biochemical response was also shown to be predictive of the overall survival in patients with medullary (calcitonin) and de-differentiated iodide-negative thyroid cancer (thyroglobulin) undergoing $^{90}$Y-DOTATOC [9, 11]. Symptomatic response, particularly durable diarrhea improvement after $^{90}$Y-DOTATOC, proved to have an impact on progression-free survival [20].

7.1.5.3. **Toxicity**

Side effects, involving kidney and bone marrow, are mild if adequate renal protection and fractionation are employed. Severe (grade 3 and 4), mostly reversible, acute bone marrow toxicity occurs in less than 10-13% following $^{90}$Y-DOTATOC and 2-3% following $^{177}$Lu-DOTATATE. Nevertheless, sporadic cases of myelodysplastic syndrome or overt acute myelogenous leukaemia have been reported [15].

The kidney represents the dose-limiting organ at the activities normally reached with PRRNT. Proper kidney protection, as described in chapter 8, is nowadays mandatory as it significantly reduces renal absorbed dose and, in turn, the risk for delayed kidney toxicity [21-23]. However, despite kidney protection, loss of kidney function can occur after PRRNT, with a creatinine clearance loss of about 3.8% per year for $^{177}$Lu-DOTATATE and 7.3% per year for $^{90}$Y-DOTATOC [24]. A 9.2% incidence of grade 4 and 5 kidney toxicity has been reported in a series of 1109 patients treated with $^{90}$Y-DOTATOC [19]. Kidney toxicity after $^{90}$Y-DOTATOC has been more frequently observed in patients with risk factors for delayed renal toxicity, such as long-standing and poorly controlled hypertension and diabetes mellitus [20].

A transient impairment of fertility was reported in males undergoing PRRNT, due to the irradiation of Sertoli cells, as testified by a transient rise in FSH and a consensual drop in Inhibin-B. Usually recovery is complete within 2 years period after the end of therapy [6].

Despite the presence of sstr in normal pituitary, thyroid, adrenals and Langerhans cells, no significant alteration of endocrine functions were reported [25].

In patients without or with minor metastatic liver involvement, no significant hepatic toxicity was reported. However, in patients with extensive metastatic liver involvement and impaired liver function, liver toxicity may occur as a serious complication that should be considered, along with pre-existing conditions affecting the liver, when choosing the appropriate radioisotope and therapy dosing. In such cases, $^{177}$Lu-labelled peptides are recommended and the administered activity should be reduced accordingly.

7.2. **Multidisciplinary approach to PRRNT**

Establishment of a tumour board entails a minimum number of specialists that should include surgeon, pathologist, oncologist, (interventional) radiologist, nuclear medicine physician, radiotherapist, endocrinologist, gastroenterologist, and all who share an interest in NETs.
The primary intent of the NET tumour board is to assist the attending physician in the prioritization of the treatment plan that may include several options and therapeutic modalities at the initiation of care for the newly referred patients.

It is understood that the primary caring physician has the privilege to return to the NET tumour board to further consultation or confirmation of treatment plan, in case of disease progression. Alternate strategies may be more appropriate in selected cases to involve additional specialists to deal with special co-morbid conditions.

Viable therapeutic approaches are the following:

a. Surgery with a curative intent should **always** be performed whenever feasible.

b. In selected cases, and within a multidisciplinary approach, PRRNT may be beneficial as a neoadjuvant therapy to render a patient accessible to surgery.

c. For functionally active tumours, cytoreductive strategies, e.g. surgery, trans-arterial chemo-embolization (TACE), trans-arterial embolization (TAE) and radiofrequency ablation (RFA) should always be considered aiming at alleviating clinical symptoms.

7.3. **Radiopharmaceuticals used for therapy**

Radiopharmaceuticals approved by national authorities for human use should be used.

7.4. **Patient eligibility for PRRNT**

7.4.1. **Inclusion criteria**

The following information is mandatory in order to perform PRRNT:

- Histo-pathology proven NET.
- High somatostatin receptor expression determined by functional whole body imaging (see chapter 5) or immunohistochemistry.

The remaining criteria should be taken into consideration when deciding on performing PRRNT.

a. **Karnofsky** Performance Status > 60 or **ECOG** <2.

b. Tumour differentiation, preferably in G1-G2.

c. Tumour proliferation rate, preferably with a Ki-67 / mitotic index ≤ 20%. In addition, the rate of tumour growth, as determined by CT or MRI, could be considered. Please note that, in general, less differentiated tumours showing high proliferation rate are good candidates for chemotherapy.

7.4.1.1. **Renal function**
Renal function should be assessed by means of laboratory tests (creatinine and BUN), calculated GFR (e.g. Cockcroft-Gault formula), or nuclear medicine methods (e.g. 99mTc-MAG3 including the determination of the TER, 99mTc-DTPA GFR or Hippuran ERPF).

For 90Y-labelled peptides age-adjusted normal renal function is essential. Patients with compromised renal function may still be considered for 177Lu-peptides.

For 177Lu-labelled peptides a mild-moderate grade of renal impairment can be tolerated (e.g. creatinine ≤1.7 mg/dl). GFR and TER should be at least 70% of mean age-adjusted normal values.

7.4.1.2. Hematological status

Non-compromised hematological reserve should be present before PRRNT:

WBC >3000/μl, PLT >75,000/μl for 177Lu-DOTATATE,
WBC >3000/μl, PLT >90,000/μl for 90Y-DOTATOC, RBC >3,000,000/μl.

7.4.2. Aggravating conditions (caveats)

The following conditions, if not attended to, can lead to serious organ damage:

a. Renal outflow obstruction, potentially leading to hydronephrosis, and, ultimately, to loss of renal function, should always be ruled out or possibly corrected before PRRNT.

b. Previous myelotoxic chemotherapy and extended radiation fields to the bone marrow (pelvis, spine), especially if performed in the weeks preceding PRRNT, impart an additional risk for post-PRRNT bone marrow failure. In questionable cases of hematologic compromise, a bone marrow biopsy might be indicated to discriminate treatable cases, especially for pre-treated patients and subsequent PRRNT cycles. Depending on the amount of 90Y-DOTATOC or 177Lu-DOTATATE activity injected, depressed platelets values following prior PRRNT cycle/s can preclude timing and dosing of the subsequent cycles.

c. Liver failure should be regarded with caution before considering PRRNT.

7.4.3. Exclusion criteria

a. Pregnancy

b. Breast feeding (if not discontinued)

c. Severe acute concomitant illnesses

d. Severe psychiatric disorders.
7.5. Implementing PRRNT

PRRNT can be administered employing fixed-activity treatment cycles or individualized dosing, adjusted on the basis of clinical parameters (body surface area, hematological or renal function, and clinical status) or dosimetry-based.

Dosimetry-based regimens are desirable; however, they are seldom feasible and in routine practice, therefore the fixed or individualized approach is commonly used.

Experiences among the different centers also showed variations in intervals, cumulative activity and radioisotopes used.

Cumulative activities for $^{90}$Y-labelled peptides were reported up to 18 GBq (~ 500 mCi), provided the renal absorbed dose (or, better, bioeffective renal dose) threshold was not exceeded.

Reported cumulative activities for $^{177}$Lu-labelled peptides were in the range of 22 to 30 GBq (~ 600-800 mCi), provided the renal absorbed dose (or, better, bioeffective dose) threshold was not exceeded.

7.5.1. Somatostatin analogues withdrawal

Somatostatin analogues are available as short-acting or long-acting preparations. These should be discontinued prior to PRRNT as they might interfere with receptor targeting. The duration of interruption, however, depends on the half-life of the analogue used. An interruption of 3-4 weeks for long-acting release formulations is considered adequate while an interruption of at least 24 hours for short-acting formulations are considered as good clinical practice. This topic is still a matter of ongoing debate.

7.5.2. Pre-medications for PRRNT

A pre-medication is required to prevent acute adverse effects caused by radiation and amino acid infusion.

Recommended medications include:

- Serotonin 5-HT$_3$ receptor antagonists, e.g. granisetron (Kytril®), ondansetron (Zofran®) or tropisetron (Navoban®) given intravenously shortly before the radiopeptide infusion. These may be repeated if required.

- Corticosteroid, e.g. dexamethasone, 4 mg or more given intravenously shortly before the radiopeptide infusion. This may be repeated if required.

For renal protection, please refer to chapter 8.

7.5.3. Treatment regimens using $^{90}$Y-DOTATATE / $^{90}$Y-DOTATOC

For the non compromised patients, the following treatment regimens are in use:

Administered activity: 3.7 GBq (100 mCi)/m$^2$ body surface

Number of cycles: 2
Time interval between cycles: 10-12 weeks.

or

Administered activity: 2.78 – 4.44 GBq (75-120 mCi)
Number of cycles: 2-4
Time interval between cycles: 10-12 weeks.

7.5.4. Treatment regimens using $^{177}$Lu-DOTATATE / $^{177}$Lu-DOTATOC

For the non-compromised patients, the following treatment regimen is in use:

Administered activity: 5.55 – 7.4 GBq (150-200 mCi)
Number of cycles: 3-5
Time interval between cycles: 10-12 weeks.

7.5.5. Combination $^{177}$Lu/$^{90}$Y-peptides therapy regimens

For the non-compromised patients, the following sequential treatment regimen is in use:

$^{177}$Lu administered activity: 5.55 – 7.4 GBq (150-200 mCi)
$^{90}$Y administered activity: 2.5 – 5.0 GBq (68 -135 mCi)
Number of cycles: 2-6
Time interval between cycles: 10-16 weeks.

Combination therapies with $^{90}$Y and $^{177}$Lu peptides are being actively investigated and may prove to have additional therapeutic benefit. However, such combination treatments should be performed in centers with sufficient competence and extensive experience with PRRNT. In this case administered activities should be adjusted on an individual basis. Concurrent therapies administering a cocktail of $^{177}$Lu and $^{90}$Y labelled peptides are also emerging.

7.5.6. Additional measures in the compromised patients

For compromised patients the administered activities are usually reduced and individualized, according to clinical/biochemical parameters or dosimetric studies.

In patients with reduced renal function the following additional interventions are used:

a. Nephro-urology consultation

b. Extensive hydration (e.g. 2-3 liter of fluid intake, if clinically appropriate) prior to PRRNT

c. Diuretics (e.g. furosemide) should be considered in case of dilated pelvis and delayed renal urinary drainage.
d. Whenever possible, consider the patient for a $^{177}$Lu-based treatment.

In patients with reduced haematological values the following additional interventions are used:

a. Haematologist consultation

b. When indicated, packed red blood cells and/or platelet concentrates to be given particularly before PRRNT

c. If needed, growth factor treatment with granulocyte stimulating factors or erythropoietin (or its derivatives) can be considered not earlier than 10 days after PRRNT.

d. In severely compromised bone marrow reserves, peripheral stem cell harvesting, as a precautional measure, could be considered before PRRNT and, if necessary, reinfusion may be performed at appropriate time distance from PPRNT.

7.5.7. Special considerations for PRRNT in children

$^{90}$Y-DOTATOC has been used in children applying the activities of 1.5-1.85 GBq/ m$^2$/cycle up to 3 cycles.

As regards the use of $^{177}$Lu-DOTATATE in children, there is no widespread experience, and activities should be adapted per meter square [26].

A more extensive description on the use of PRRNT in paediatric patients is provided in Chapter 3.

7.5.8. Retreatment options

The decision of re-treating a patient with PRRNT should be taken within the framework of the tumour board. In patients who previously responded to PRRNT, re-treatment may be considered in case of well-documented disease progression.

This new PRRNT course will follow the same eligibility criteria as previously described for the first radiopeptide treatment.

The options include the use of the same or a different radiopeptide. For instance, choosing $^{177}$Lu-labelled peptides may be warranted, especially when considering the preservation of kidney function. When designing a re-treatment, caution should be given to the possibility of trespassing renal threshold, dose especially in patients with a good prognosis and long survival expectancy.
REFERENCES


8. EVALUATION OF RESPONSE

The evaluation of treatment response includes consideration of the clinical, biochemical, morphological and functional status, and the well-being of the patient.

For clinical and biochemical evaluations, please refer to Chapter 2. For evaluating the quality of life (QoL), please refer to the QoL forms provided by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 using the following link: [http://groups.eortc.be/qol/questionnaires_downloads.htm](http://groups.eortc.be/qol/questionnaires_downloads.htm).

Morphologic (or anatomic) response is determined by the acquisition of morphologic and/or anatomic sequential imaging studies using ultrasound, contrast-enhanced CT, or MRI. Criteria to determine the objective response are provided by the WHO, SWOG and RECIST. For assessing response, CT is the preferred imaging technique, but MR imaging is also of great value, when available. In some cases, CT and MRI can be complementary. In any case, the same imaging technique should be applied to follow individual patients. The interval of the follow-up depends on the disease duration and tumour biology, commonly these examinations are performed at 3-6 months initially, the interval may be extended to 12 months during follow-up.

Since 1979, the WHO attempted to define criteria for assessing objective response. Later on, in 1992, criteria set up by the South Western Oncology Group (SWOG) defined the magnitude of objective response as: complete response, partial response, stable disease, or progression. These categories were based on the change of the tumour load, that is calculated by adding the sum of the products of maximum perpendicular diameters for all assessable lesions [1, 2].

The recently introduced RECIST 1.0 and 1.1 criteria (2010) attempted to simplify and standardize the former complex SWOG criteria of assessing response. The RECIST criteria require a measurement of the longest diameter or sum of the two longest diameters of a particular lesion(s) [3]. Currently, this is the preferred method applied in clinical trials to assess tumour response.

When assessing growth rate of NETs, a combination of functional and morphological imaging techniques provides in the majority of cases better insight into the true behaviour of the tumour under treatment. Such hybrid imaging approaches may include somatostatin receptor SPECT/CT applying Tc-99m or In-111 or if available, somatostatin receptor imaging PET/CT using 68Ga-DOTA-peptides. Functional imaging is an invaluable instrument for assessing tumour biology in the course of the disease as it capable of predicting the morphologic response [4], yet, it is not accepted as a substitute to the anatomic for this purpose.
REFERENCES


9. PRACTICAL ASPECTS OF PRRNT

9.1. Facility

The facility design and equipment will depend on the national legislation regulating the use of therapeutic radioactive agents.

9.2. Administration of therapeutic radiopharmaceuticals

During the administration of the radiopharmaceutical a medical doctor must remain in close proximity. A resuscitation cart as well as a trained emergency team must be available. Radiopharmaceutical should be diluted with saline to a final volume ranging from 10 - 100 ml, depending on the infusion system used. Radiopharmaceutical should be administered via an indwelling catheter over 10 to 30 minutes, depending on the infusion system used. Radiopeptide may be co-infused with amino acid solutions via a three-way stop-cock (“piggy-back”). The line should be flushed with saline after the completion of radiopeptide infusion.

PRRNT infusion may provoke and reproduce the syndromes of the respective functional tumours due to tumour receptors’ stimulation and the sudden substantial release of hormones. The clinical manifestation dependends on the specific hormone involved. The following percautious measures are therefore recommended:

Blood pressure and pulse should be monitored at short intervals prior, during and after therapy infusion, giving special attention to symptomatic patients. The required medications should be available and in close vicinity to allow immediate treatment of acute paraneoplastic symptoms. The risk group of patients, likely to exacerbate, are those with known functioning NET resulting in any of the following syndromes; carcinoid syndrome-hypotension, hypoglycemia, hypergastrinemia, hypertension, hypotension, Watery Diarrhea Hypokalemia Achlorhydria syndrome or electrolyte imbalance.

For a comprehensive classification of adverse effects, please refer to “Common terminology criteria for adverse events v3.0 (CTCAE) provided under the following link: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Patients presenting with urinary incontinence are to be catheterized prior to PRRNT administration. The catheter should remain in place for 2 days.

After treatment, female patients should avoid pregnancy for at least 6 months. Male patients should consider sperm banking before therapy.

9.3. Renal protection

9.3.1. Physiology of renal irradiation by PRRNT

The kidneys are the critical organs in PRRNT. Proximal tubular reabsorption of the radiopeptide and the subsequent retention in the interstitium results in renal irradiation. Nephrotoxicity is accelerated by risk factors, such as pre-existing hypertension or diabetes [1]. To counteract and reduce the high kidney retention of radiopeptides, positively charged molecules, such as L-lysine and/or L-arginine, are commonly used to competitively inhibit the proximal tubular re-absorption of the radiopeptide. Extensive experience supports the utilization of positively charged amino acids, both in animals and in humans. The co-administration amino acids resulted in a significant reduction of the renal irradiation absorbed
dose ranging from 9 to 53% [2]. The absorbed renal irradiation dose is further reduced by up to 39% when extending the infusion time of the amino acid solution to 10 hours and by up to 65% by providing aminoacid infusion over two days following radiopeptide administration, thereby covering more efficiently the renal elimination phase of the radiopeptide [3, 4].

Due to the beta emission characteristics of the two radionuclides, renal absorbed dose is higher for $^{90}$Y-labelled peptides than for the $^{177}$Lu-labelled ones.

Different regimens of amino acid co-infusion were used by various groups, leading to a 27% mean reduction of the renal absorbed dose (range 9–53%), but not effecting receptor targeting or tumour uptake [2]. The use of amino acids, therefore, permits a safe administration of higher activities leading to deliver potentially tumorocidal irradiation doses. Side-effects such as nausea, headache, and rarely vomiting, are associated with the amino acid induced metabolic acidosis, these symptoms do occur in the majority of patients [5, 6].

To exert a protective effect on the kidney, sufficient mass of positively charged amino acids, at least 25 g as cumulative amount, should be infused. In this respect, it should be noted that solutions containing only few grams of Lysine or Arginine are not effective and this practice should avoided.

9.3.2. Amino acids protection protocols

Lysine and/or Arginine should be diluted appropriately in large volumes of normal saline in order to hydrate the patient. Concentrated solutions should be avoided, as they might induce dangerous electrolyte imbalances leading to severe metabolic acidosis and cardiac arrhythmias. The minimum recommended and appropriate dilution is 25 g of amino acid in 1 liter of normal saline.

Prior to proceeding with amino acid infusion, appropriate measures to encounter nausea and vomiting should include the administration of corticosteroids and antiemetics, as described in details in Chapter 7. Amino acid infusion should be started 30-60 minutes before the administration of the radiopeptide and maintained over four hours thereafter. Studies showed that prolonging infusion over 10 hrs [3] or repeating the short protocol during the following two days allows achieving higher renal protection [4]. Particular attention and care should be given to possible electrolyte imbalance, namely hyperkalemia, hypernatriemia, and the consequent metabolic acidosis that commonly lead to mild nausea and vomiting. The latter side effects should be managed by hydrating the patient with normal saline and possibly repeating corticosteroid or antiemetic administrations.

Proposed amino acid protective schemes:

9.3.2.1. Single day 50 grams protection protocol

A solution containing a 50 g cocktail of Lysine and Arginine (25 g of Lysine and 25 g of Arginine) diluted in 2 liters of normal saline infused over 4 hours, starting 30-60 minutes before PRRNT.

9.3.2.2. Three days 25 grams protection protocol

During day 1 a cocktail of 25 g of Lysine diluted in 1 liter of normal saline infused over 4 hours, starting 30-60 minutes prior to the PRRNT. This is followed by the administration of a 12.5 g Lysine solution in 500 ml of normal saline, over 3 hrs, twice a day on the second and
third day post-therapy. This protocol is aimed at maximizing renal protection while minimizing side effect of the amino acid infusion.

9.3.2.3. *Three days 50 grams protection protocol*

A solution 50 g (25:25 gr) Lysine:Arginine solution diluted in 2 liters normal saline infused over 4 hours during the first day, starting 30-60 min before therapy. This is followed by the administration of an additional 12.5 g Lysine diluted in 500 ml of normal saline, infused over 3 hrs, twice a day on day 2 and day 3 post-therapy.

9.3.2.4. *50 g Amino acids + gelofusine single day*

A combination of 25 g Lysine + 25 g Arginine diluted in 2 liters of normal saline infused over 4 hours, starting 30-60 min before, and Gelofusine infusion as a bolus of 1 ml/kg body weight (BW) over 10 minutes before therapy, followed by Gelofusine infusion at 0.02 ml/kgBW/min over 3 hours after radiopptide infusion.

Due to reported adverse immunogenic reactions, patient monitoring during gelofusine infusion, including vital parameters (blood pressure and pulse), as well as clinical conditions, should be performed [7].

9.3.3. *Gelofusin renal protection protocol*

The renal uptake of radiolabelled somatostatin analogues is partly associated with the megalin/cubilin system. Gelofusine®, is a ready for infusion solution containing 4% succinylated (or modified fluid) bovine gelatin, sodium hydroxide and water for injection. It is used as a plasma expander, can be applied to further reduce kidney absorbed radiation dose by about 45% [8]. There have been some safety concerns about the use of Gelofusin due to a relatively high incidence of allergic reactions, although mild in most cases [9]. The treating physician should be aware of these effects and be prepared to treat them accordingly with anti-histamine drugs, corticosteroids or epinephrine.

Since this regimen has been used in a large series of patients, no serious kidney toxicity has occurred. Mild to moderate allergic side effects, as scaled by the ‘common toxicity criteria’ (CTC) of grade 1 or 2 applying the kidney protective regimen, were recorded in 1.4% of courses, and grade 3 CTC reactions occurred in 0.6%. In addition, extensive experience with the administration of succinylated gelatin to patients in acute care or during surgical procedures exists and serious side effects are very rare. Severe anaphylactoid reactions are described in approximately 0.04% [10].

9.3.4. *Precautions in special clinical conditions*

In patients with severe cardiac insufficiency, volume overload that might lead to acute cardiac insufficiency and decompensation should be avoided. Therefore, formulations with lower amounts of amino acids and hence lower volumes should be chosen (e.g. 25 g of Lysine or Arginine diluted in maximum 1 liter of normal saline). In any case, a stringent monitor with the involvement of the cardiologist is recommended.

In patients with pre-existent nephrolitiasis, forced diuresis might mobilize kidney stones, leading to acute renal colic. These events should be treated accordingly but, if possible, anticipated and avoided by infusing lower volumes.
Phlebitis at the site of injection, associated with the hyperosmolarity of the infused amino acids solution, may occur. This effect can be treated with local vaso-protective creams.

9.4. Post-therapy imaging

Using $^{177}$Lu-labelled peptides, whole body imaging should always be performed following each treatment cycle to document the targeting and distribution of the radiopharmaceutical and to judge the functional response to PRRNT.

9.4.1. $^{177}$Lu-DOTATATE

Planar images should be obtained with a double-headed gamma camera, equipped with parallel-hole medium-energy collimators utilizing the higher gamma-emission peak at 208 keV with a window width of 15%. Whole-body scanning time of 30 minutes is recommended, while spot view scanning time can be limited to 5 minutes. A reference radioactivity source containing approximately 200µCi in about 20 ml vial, should be prepared on the day of injection and scanned simultaneously alongside the patient’s head.

ROIs of the kidneys and, if possible, of a measurable tumour site should be drawn, and CT based volumetry followed by dosimetric calculations may be performed.

After the first treatment: whole-body images or spot views of the upper abdomen and all involved sites should be acquired at 3 time-points, preferably at day 1, 4 and 7 p.i.

SPECT can be obtained at any day for better topographic comparison with CT/MR images.

For the following treatments, acquire whole-body or spot views of the upper abdomen and other sites of interest. SPECT is optional at 2 time-points after treatment, preferably day 1 and 4 p.i.

9.4.2. $^{90}$Y-DOTATOC

Using $^{90}$Y-labelled peptides, the imaging of Bremsstrahlung is performed to assess the distribution of radioactivity, although image quality is rather poor.

The radionuclide $^{90}$Y is a rare-earth metal that chemically belongs to the lanthanides. It emits $\beta$-particles with mean electron energy of 0.935 MeV and a maximum energy of 2.3 MeV, and has a half-life of 64.1 h. The absence of gamma emission from $^{90}$Y does not permit direct imaging useful for diagnostic and dosimetry purposes, although poor quality images can be obtained from the Bremsstrahlung (braking radiations) of $\beta$-particles.

For diagnostic and dosimetric purposes $^{111}$In has been introduced in clinical practice as a substitute tracer because of its similar chemical properties. Alternatively, when available, the positron emitter isotope $^{86}$Y, same chemical element, has been used for PET imaging and dosimetry for research purposes.

However, pure Bremsstrahlung whole-body imaging is usually performed at 24 h after $^{90}$Y-DOTATOC administration injection in order to evaluate the radioactivity distribution throughout the body. Quantification of radionuclide content in organs and tumours is usually rough and the accuracy depends upon the correction for photon attenuation and collimator response. Nevertheless, these images allow obtaining a rough estimation of the biodistribution of radioactivity.
In order to achieve a clinical compromise between sensitivity and resolution, gamma cameras equipped with a 3/8” (0.95 cm) NaI(Tl) crystal and medium-energy general purpose collimators with wide-energy window (25-285 KeV) are generally accepted [11].

To exclude the X-ray characteristic emission, gamma cameras equipped with 1” (2.54 cm) NaI(Tl) crystals and high-energy general purpose collimators can be used with a 60% energy window centered at 150 keV with a range between 105-195keV [12].

9.5. Post-therapeutic monitoring and management

The evaluation of renal function is extremely important, as the kidney is the critical organ in PRRNT. The follow-up should at least include the evaluation of serum creatinine levels and the determination of creatinine clearance. In patients with pre-existing risk factors for delayed renal toxicity (high-risk group), in particular long-standing and poorly controlled hypertension and diabetes mellitus, single kidney or previously known insults to the kidneys, particularly nephrotoxic chemotherapy, more precise methods to assess renal function are recommended. These techniques may include GFR measurements by $^{99m}$Tc-DTPA, $^{51}$Cr-EDTA or measurement of $^{99m}$Tc-MAG3 clearance.

The National Cancer Institute (NCI) toxicity criteria for bone marrow and kidney function are presented in Tables 9.1 and 9.2.

9.5.1. In between cycles

A complete blood cell count should be determined every 2-4 weeks. A higher frequency can be adopted, if clinically required. Renal and liver function tests should be available before confirming subsequent cycles.

Following careful clinical evaluation, patients having blood values lower than the limits indicated for the first PRRNT cycle should receive a lower activity, and/or next the PRRNT cycle should be postponed. In severe cases, interruption of PRRNT should be considered.

9.5.2. Intermediate and long-term follow-up

A complete blood cell count, renal and liver function should be determined every 8-12 weeks for the first 12 months, and twice a year thereafter, if clinically indicated.
TABLE 9.1. SUMMARY OF THE BONE MARROW TOXICITY ADAPTED FROM COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS v3.0 (CTCAE) Published by the National Cancer Institute August 9, 2006

<table>
<thead>
<tr>
<th>Bone Marrow</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event long Name</strong></td>
<td>1</td>
</tr>
<tr>
<td>Bone marrow cellularity</td>
<td>Mildly hypocellular or ≤25% reduction from normal cellularity for age</td>
</tr>
<tr>
<td>CD4 count</td>
<td>&lt;LLN – 500/mm³</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>&lt;LLN</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt;LLN – 10.0 g/dL</td>
</tr>
<tr>
<td>Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)</td>
<td>Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'], schistocytes)</td>
</tr>
<tr>
<td>Iron overload</td>
<td>—</td>
</tr>
<tr>
<td>Leukocytes (total WBC)</td>
<td>&lt;LLN – 3000/mm³</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>&lt;LLN – 3.0x10⁹/L</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>&lt;LLN – 800/mm³</td>
</tr>
<tr>
<td></td>
<td>&lt;LLNx 0.8 – 10⁹/L</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td>&lt;LLN – 1500/mm³</td>
</tr>
<tr>
<td></td>
<td>&lt;LLN – 1.5 x 10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;LLN – 75,000/mm³</td>
</tr>
<tr>
<td></td>
<td>&lt;LLN – 75.0 x 10⁹/L</td>
</tr>
<tr>
<td>Splenic function</td>
<td>Incidental</td>
</tr>
<tr>
<td></td>
<td>findings</td>
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<tr>
<td></td>
<td>(e.g.,</td>
</tr>
<tr>
<td></td>
<td>Howell-Jolly</td>
</tr>
<tr>
<td></td>
<td>bodies)</td>
</tr>
<tr>
<td>Blood/Bone Marrow –</td>
<td>Mild</td>
</tr>
<tr>
<td>Other (Specify, __)</td>
<td></td>
</tr>
</tbody>
</table>

LLN: lower limit of normal values
### TABLE 9.2. SUMMARY OF RENAL TOXICITY ADAPTED FROM COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS v3.0 (CTCAE)

Published by the National Cancer Institute August 9, 2006,

<table>
<thead>
<tr>
<th>Kidney Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td><strong>Adverse Event long Name</strong></td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
</tbody>
</table>

**REMARK:** Adjust to age-appropriate levels for pediatric patients. **ALSO CONSIDER:** Glomerular filtration rate.

<table>
<thead>
<tr>
<th>Glomerular filtration rate</th>
<th>GFR</th>
<th>&lt;75 – 50% LLN</th>
<th>&lt;50 – 25% LLN</th>
<th>&lt;25%, chronic dialysis indicated</th>
<th>LLN, not indicated</th>
<th>Chronic dialysis or renal transplant indicated</th>
<th>Death</th>
</tr>
</thead>
</table>

**ALSO CONSIDER:** Creatinine.

**ULN:** upper limit of normal value for age
REFERENCES


10. DOSIMETRY

10.1. Introduction

Whenever possible, patient-specific dosimetry should be performed to allow assessing organ absorbed dose and to possibly predict the risk of delayed renal toxicity.

Different dosimetry methods, practical or sophisticated, can be applied depending on purposes and availability of resources. Input data includes blood and urine samples, and scintigraphic images adequately scheduled up to 3 days p.i. Planar images are useful to derive biokinetics over time, while SPECT and SPECT/CT fused images, although more time-consuming, permit detailed insight over intra-organ activity distribution. The MIRD scheme represents the reference formalism for internal dosimetry. Dedicated software (OLINDA/EXM) has been used to derive mean absorbed dose estimates for $^{177}$Lu- and $^{90}$Y-peptides (Annex I).

10.2. Biological Effective Dose (BED) concept

Kidney radiation toxicity is typically evident several months after irradiation due to the slow repair characteristics of renal cell. According to studies on renal toxicity derived from external radiotherapy, the accepted renal tolerated dose is in the range of 23-25 Gy. As stated by the National Council on Radiation Protection and Measurements (NCRP), in fact, a dose of 23 Gy to the kidneys causes detrimental deterministic effects in 5% of patients within 5 years [1]. Nevertheless, clinical experience and dosimetric studies clearly indicate that this renal dose threshold does not accurately correlate with the renal toxicity observed in patients undergoing PRRNT [2]. PRRNT is a form of continuous radiation delivery with a decreasing dose-rate with time. The irradiation produces both lethal and sub-lethal damage that can be repaired during the irradiation itself, but the differential between creating new damage and the repairing depends on the specific dose-rate at any particular time and on the repair capability ($T_{1/2}$ rep.) of the tissue. Low dose-rates, as in PRRNT, will spare normal tissue more than the tumour, and this may allow benefits as in fractionation in external radiotherapy [3]. The linear quadratic model interprets mathematically this differential sparing. The biological effective dose (BED) concept is used to quantify the biological effects induced by different patterns of radiation delivery. This model has been recently revised for radionuclide therapy and applied in particular to PRRNT with the intent of enhancing the dose-response correlation [4]. Focusing on the kidney concern, the BED has proven to be a reliable predictor of renal toxicity, helpful in the implementation of individual treatment planning [5].
REFERENCES


ANNEX I. DOSIMETRIC METHODS

Dosimetry of normal organs and malignant lesions represents a fundamental aid in the planning of PRRNT in order to deliver the maximum dose to the tumour while remaining within the therapeutic window as regards the dose delivered to the normal organs, particularly the kidney, the dose limiting organ, and the bone marrow.

Dose estimates in organs for PRRNT are generally performed using the MIRD scheme, with the basic formula \( D = \bar{A} \times S = A_0 \times \tau \times S \), where \( \bar{A} \) is the integral activity in the organ, \( A_0 \) is the initial activity in the organ, \( \tau \) is the residence time corresponding to the total number of decays occurring in the organ, and \( S \) is a factor depending on the properties of radionuclide and the target. Once the integral activities in organs of interest are determined by numerical or compartmental models [1, 2], absorbed dose calculations are generally performed using dedicated softwares that consider as input the residence time \( \tau \) or ND (OLINDA/EXM, RADAR – [3,4]).

The typical kinetics of radiopeptides, namely the very fast blood clearance and renal elimination, determine the information required to obtain the integral activities in organs and tumour, which include a whole dataset of scintigraphic images and a blood and urine collection. Once the rough data are analysed, the activity in normal and tumour tissues has to be converted into time-activity curves, and the absorbed doses finally estimated.

Specifically, the essential data required are blood samples (preferably 3 - 4 samples within the following time intervals: 0-1 h; 1-5 h; 5–24 h; 24-72 h p.i.), a complete urine collection within pre-selected time intervals, and scintigraphic images (anterior and posterior whole body (WB) and SPECT acquisitions). Although, in principle, planar views are not ideal for dosimetry, the availability of 5-7 WB serial images (2-3 h p.i. up to almost 3 days p.i.) might offer complete and satisfactory information on biodistribution and its variation in time [5, 6].

The calibration of the system can be performed by means of absolute or relative calibration methods. The first uses a known source to obtain a factor that converts the counts for unit time in activity; the latter normalizes the counts per unit time of the first total body image to the 100% of activity.

To evaluate the biodistribution in the source organs, total body images are analysed by the conjugated view method. Regions of interest (ROIs) are drawn over the total body, tumour and normal organs – heart, lungs, liver, spleen and kidneys. The same set of ROIs must be used for all the performed scans. Collected data must then be corrected for background, attenuation, scatter and physical decay in order to obtain the time-activity curves. To evaluate the kinetics of the system, a compartment model can be used. The SAAM II programme can be applied to fit the observed data in the compartment model [2].

The residence time for the red marrow is calculated from the residence time in blood, with the assumption of non-specific uptake of the radiolabel in the bone marrow. A uniform activity distribution and an equivalent clearance in red marrow and blood are assumed. Due to the small size of the radiopeptide, the specific activity in bone marrow can be considered equal to the specific activity in blood [7, 8]. To calculate the absorbed dose to the bladder wall, the residence time for bladder contents is calculated following the dynamic urinary bladder model [9] based on the experimental curve of the cumulative activity eliminated in the urine. The bladder can be assumed to be voided first at fixed intervals, e.g. 0.5 h and 3 h after injection, and then at 4.8 h intervals thereafter. Residence times for tumour are also calculated from the
tumour time-activity curves. Tumour-absorbed doses can be then evaluated by approximating the lesion to a spherical shape and considering a uniform activity distribution [10]. In the case of $^{90}$Y-DOTATOC, the lack of $\gamma$-emission of $^{90}$Y does not allow direct dosimetry. Bremsstrahlung images are, in fact, rather difficult to analyze quantitatively, and two alternative options have been introduced in clinical practice, the $^{111}$In and the $^{86}$Y simulations.

For dosimetric purposes $^{111}$In-DOTATOC has been introduced in clinical practice as a substitute tracer because of its similar chemical properties.

The $^{111}$In physical half-life being almost identical to that of $^{90}$Y and also compatible with the kinetics of peptides, the diagnostic activities usually administered ($\sim$185 MBq) allow collecting serial images (planar and SPECT) for a suitable period of time (easily over 3-4 days).

An alternative solution, at least theoretically, is the use of DOTATOC labelled with the positron emitter isotope $^{86}$Y, the identical chemical element of the therapeutic counterpart. The DOTATOC peptide labelled with $^{86}$Y totally preserves the chemical nature of $^{90}$Y-derivatives and offers a nice spatial resolution due to the possibility of PET imaging. Nevertheless, limitations, mainly related to the short time interval (<24-40 h) available for data collection, due to the short physical half-life of 14.7 h and the low positron abundance, high cost, and low availability indeed exist.

Despite advantages and drawbacks of the two above-mentioned methods, the extrapolated absorbed doses are reasonably similar.

It has to be specified that both $^{111}$In-pentetreotide scintigraphy and $^{68}$Ga-DOTATOC PET are not suitable for a correct dosimetric analysis; the first due to its different kinetics and receptor affinity properties, and the latter compound due to the too short physical half-life (68 minutes) of $^{68}$Ga, as compared to the biological half-life of DOTATOC and also to possible different chemical properties and behavior, as compared to the $^{90}$Y counterpart.

Recently, a new potentiality of $^{90}$Y-imaging has emerged, pointing out the possibility of omitting simulations by $^{111}$In or $^{86}$Y-imaging [11-13].

In the case of $^{177}$Lu-DOTATATE, the $\gamma$ photons emitted by $^{177}$Lu are suitable for scintigraphy, enabling both imaging and dosimetry with the same compound. Being the treatment repeated in multiple cycles, dosimetry is usually performed directly during the first courses of therapy, after the administration of therapeutic activities of $^{177}$Lu-DOTATATE.
TABLE I-1. INFORMATION AND DATA TO BE COLLECTED TO PERFORM DOSIMETRIC ANALYSIS AND SELECTED RELEVANT ADDITIONAL READINGS*

<table>
<thead>
<tr>
<th>DATA COLLECTION</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>blood sample (e.g. 1 ml) collection with time schedule for fast clearance (e.g.: at 5, 10, 20, 30 min, and 1, 4, 6, 16, 20, 28, 44, 52 h p.i.)</td>
</tr>
<tr>
<td>Urine</td>
<td>complete urine collection up to 48-64 h p.i. at established time-intervals (e.g.: 0-1; 1-3; 3-6; 6-16; 16-24; 24-40; 40-48; 48-64 h p.i.).</td>
</tr>
<tr>
<td><strong>Morphological Imaging</strong></td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>close to the date of therapy</td>
</tr>
<tr>
<td><strong>Functional Imaging</strong></td>
<td></td>
</tr>
<tr>
<td>Whole body transmission</td>
<td>before administration</td>
</tr>
<tr>
<td>Whole body scintigraphy</td>
<td>at least 4 - 5 acquisitions (e.g. at 1; 3-4; 16-24; 40-48; 64-80 h p.i.)</td>
</tr>
<tr>
<td>SPECT (SPECT-CT)</td>
<td>if possible, at least one additional acquisition at 16-24 h p.i. (especially at the level of the kidneys)</td>
</tr>
</tbody>
</table>

TABLE I-2. DATA PROCESSING AND CORRESPONDING LITERATURE TO EXTRACT NUMERICAL DATA FOR DOSIMETRIC PURPOSES

<table>
<thead>
<tr>
<th>DATA PROCESSING</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Image analysis</strong></td>
<td></td>
</tr>
<tr>
<td>ROIs around source organs and tumours in planar (conjugate view method) and</td>
<td>1, 2,</td>
</tr>
<tr>
<td>SPECT images.</td>
<td>12,16-18</td>
</tr>
<tr>
<td>Counts converted to activity after correction for background, scatter,</td>
<td></td>
</tr>
<tr>
<td>attenuation, and physical decay.</td>
<td></td>
</tr>
<tr>
<td>Time activity curves for the source organs (i.e. spleen, kidneys, liver, testes,</td>
<td>1, 2, 5</td>
</tr>
<tr>
<td>total body, blood, urinary bladder contents) and tumours.</td>
<td></td>
</tr>
<tr>
<td>Integral activity $A_t$ for the sources (area under time-activity curves by</td>
<td></td>
</tr>
<tr>
<td>analytical methods or compartmental models)</td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES


ANNEX II. STRUCTURED CLINICAL HISTORY FORM FOR NET PATIENTS (EXAMPLE)

<table>
<thead>
<tr>
<th>Patient’s Name</th>
<th>Visit date</th>
</tr>
</thead>
</table>

**Family history (related to cancer)**

- [ ] no
- [ ] yes
- [ ] MEN syndrome or other genetic disorders

**Past medical history (e.g. major surgery, infections, cardiovascular events, etc.)**

- Renal diseases: [ ] no, [ ] yes
- Diabetes: [ ] non, [ ] yes, first diagnosis (mm yy)_______
- Oral medication: [ ] no, [ ] yes, Insulin: [ ] no, [ ] yes
- Hypertension: [ ] non, [ ] yes, first diagnosis______(mm yy)
- Biphosphonates: [ ] no, [ ] yes

**Tumour history (NET primary / dd yy of initial surgery/biopsy)**

- Primary site (e.g. pancreas, midgut)
- Histolopathology (detailed grading, etc.):
- Immunohistology (Cg-A / synaptophysin, etc.)
- Proliferation index (Ki-67/MiB1)
- TNM stage

**Previous therapy**

- Surgical Interventions (date): [ ] no, [ ] yes (date, PT, Met)
- Biotherapy (octreotide, interferon etc.): [ ] no, [ ] yes (from / to)________________
  Specify________________________________________________________________________
- Molecular targeted therapy (everolimus, kinase inhibitors)
  Specify________________________________________________________________________
- Chemotherapy: [ ] no, [ ] yes from / to _________________
- Regional therapy (e.g. RFA, TACE, SIRT): [ ] no, [ ] yes (date, type)
Vital signs / clinical symptoms

Size _____ cm  Weight _____ kg  BMI _______

☐ loss (____ kg in ____ months)  ☐ gain (____ kg in ____ months)  ☐ constant

Flush  ☐ no flushing  ☐ <1x/week  ☐ 1-5x/week
☐ > 1-5x/day  ☐ > 5 x/day, permanent flushing

Diarrhea  ☐ no diarrhea, normal consistency
☐ Frequency (1-2x/d)  ☐ 3-5x/day
☐ 5-7x/day  ☐ 7-10x/day  ☐ >10/day

Wheeze  ☐ no  ☐ yes  Night sweats  ☐ no  ☐ yes

Dyspnea  ☐ no  ☐ yes  Dyspnea upon exertion  ☐ no  ☐ yes

Edema  ☐ no  ☐ yes (pretibial)

Pain  ☐ no  ☐ rarely  ☐ frequent/analgetics use
☐ requiring analgetics, controlled
☐ requiring analgetics, uncontrolled
☐ stable  ☐ increasing  ☐ decreasing

Pain site (main) __________________________________________

Fatigue  ☐ decreased energy non-compromising
☐ mildly incapacitating
☐ disabling

Other major symptoms __________________________________________

Medication  ☐ none  list current medications
...........................................................................

Somatostatin analogs, e.g.

Octreotide (e.g. Sandostatin)  ☐ no  ☐ yes

Lanreotide (e.g. Somatuline)  ☐ no  ☐ yes  Other____________________

Dosing mg __________ Dosing interval (weeks) __________

Last injection on (dd mm yy) __________
Subcutaneous dosing _______ µg/day, last on_________ at __________ (dd mm yy hh)

**Physical examination**

- [ ] not performed
- [ ] unchanged as compared to previous
- [ ] changes occurred compared to previous examination

<table>
<thead>
<tr>
<th>Region</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head / neck region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thorax normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological status normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karnofsky Performance Score</td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>or ECOG scale or WHO score (0-4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Previous imaging studies / diagnostics** (last 6-12 months)

☐ no imaging studies performed over the last 6 months

<table>
<thead>
<tr>
<th>Procedure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ no</td>
<td>☐ yes/date ______</td>
<td>☐ normal</td>
</tr>
<tr>
<td>Thorax CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ no</td>
<td>☐ yes/date ______</td>
<td>☐ normal</td>
</tr>
<tr>
<td>Abdomen CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ no</td>
<td>☐ yes/date ______</td>
<td>☐ normal</td>
</tr>
<tr>
<td>Abdomen MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ no</td>
<td>☐ yes/date ______</td>
<td>☐ normal</td>
</tr>
<tr>
<td>Abdomen ultrasound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ no</td>
<td>☐ yes/date ______</td>
<td>☐ normal</td>
</tr>
<tr>
<td>Bone scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ no</td>
<td>☐ yes/date ______</td>
<td>☐ normal</td>
</tr>
<tr>
<td>PET/CT:</td>
<td>☐ no</td>
<td></td>
</tr>
<tr>
<td>☐ $^{18}$F-FDG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ $^{68}$Ga-peptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ $^{18}$F-DOPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ date</td>
<td>☐ no</td>
<td>☐ normal</td>
</tr>
<tr>
<td>OctreoScan®</td>
<td>☐ no</td>
<td></td>
</tr>
<tr>
<td>☐ date</td>
<td>☐ no</td>
<td>☐ normal</td>
</tr>
<tr>
<td>MIBG Scan</td>
<td>☐ no</td>
<td></td>
</tr>
<tr>
<td>☐ date</td>
<td>☐ no</td>
<td>☐ normal</td>
</tr>
</tbody>
</table>

☐ Gastroscopy

☐ no ☐ yes/date ______ | ☐ normal  | ☐ pathological findings |

☐ Colonoscopy

☐ no ☐ yes/date ______ | ☐ normal  | ☐ pathological findings |
☐ Other examinations (e.g. Echo-endoscopy /date/ path. findings

**Blood tests/date**

☐ Blood counts Hb _____ RBC _____ WBC _____ PLT ______

☐ Renal parameters Creatinine ______ BUN __________

☐ Liver enzymes Alk. Phosphatase_____ ALT(GOT)_____ AST (GPT)

☐ Liver function test Albumine ______(g/l) INR/PT ______

**Tumour markers**

Cg-A _____ (unit)____ (normal values ____ ) date ______

Serotonin ______ µg/l (normal values ____ ) date ______

24-h urine %-5-HIAA_____ mg/24h (normal values) date________

Specific peptide hormones (e.g. gastrin, glucagon, insulin, proinsulin, VIP, etc.)

___________________________________________________ (unit)
## ANNEX III. KARNOFSKY INDEX AND LANDSKY PLAY SCALE

<table>
<thead>
<tr>
<th>General category</th>
<th>KI %</th>
<th>Specific criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to carry on normal activity</td>
<td>100%</td>
<td>Normal general status - No complaint - No evidence of disease.</td>
</tr>
<tr>
<td>No special care needed</td>
<td>90%</td>
<td>Able to carry on normal activity - Minor sign of symptoms of disease.</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>Normal activity with effort, some signs or symptoms of disease.</td>
</tr>
<tr>
<td>Unable to work</td>
<td>70%</td>
<td>Able to care for self, unable to carry on normal activity or do work.</td>
</tr>
<tr>
<td>Able to live at home and care for most personal needs</td>
<td>60%</td>
<td>Requires occasional assistance from others, frequent medical care.</td>
</tr>
<tr>
<td>Various amount of assistance needed</td>
<td>50%</td>
<td>Requires considerable assistance from others; frequent medical care.</td>
</tr>
<tr>
<td>Unable to care for self</td>
<td>40%</td>
<td>Disabled, requires special care and assistance.</td>
</tr>
<tr>
<td>Requires institutional or hospital care or equivalent</td>
<td>30%</td>
<td>Severely disabled, hospitalization indicated, death not imminent.</td>
</tr>
<tr>
<td>Disease may be rapidly progressing</td>
<td>20%</td>
<td>Very sick, hospitalization necessary, active supportive treatment necessary.</td>
</tr>
<tr>
<td>Terminal states</td>
<td>10%</td>
<td>Moribund</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>Dead</td>
</tr>
</tbody>
</table>
ANNEX IV. THE INFORMED CONSENT

Background

A written voluntary informed consent must be obtained prior to the delivery of the PRRNT for each individual cycle. Prior to implementing the PRRNT for patients, the treatment protocol alongside with a copy of the informed consent form must be approved by the Medical Ethics Committee in charge.

No patient may be treated unless her/his informed consent has been obtained.

The Nuclear Medicine physician (or legally authorized representative) should explain to the patient the nature of the therapy, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved as well as any known discomforts or untoward side effects or complications that may arise. Patients must be informed of their right to ask and withdraw of their consent, at any time, thereby to discontinue the treatment, and that this action will not affect their right to qualitative medical treatment or any other disadvantages.

The informed should be written in a simple and understandable language for the lay person. The patients should have the opportunity to closely read and consider the informed consent form prior to signing. Pending questions should always be answered in advance by the responsible physician. Oral explanation by the physician, although complementary, does not substitute for the written form.

If receiving a written consent is not possible, oral consent can be obtained if witnessed by one or more persons who will sign a statement explaining the inability of the patient to sign the consent form.

A proposed informed consent form should comply with all/any local regulatory requirements appropriate to the respective institution, government or country and the delivery of the treatment and the follow-up of the patients should comply with the Helsinki declaration for proper conduct in Medical clinical research.

ELEMENTS OF INFORMED CONSENT

The key elements of an Informed Consent form are listed herewith to assist and guide professionals considering installing PRRNT at their facility.

This should include the following points:

1. A statement that PRRNT was an option of care chosen by the patient’treating physician in agreement with the NM team and or a decision (recommendation) given by the multidisciplinary team
2. The rationale for this specific treatment option
3. An explanation about the indications for PRRNT in tailored to the patient’s disease and clinical condition
4. An explanation about the purposes of the particular treatment procedure/radiopharmaceutical
5. A description of any possible short-term side-effects or discomfort related to the administration of the radiophosphate or any of the kidney protection drugs used and their probability to occur, mentioning the source of this data.
6. A description of the possible medium and long-term complications as well as their probability of happening (mentioning the source of this data)
7. Discuss appropriate counteractions to be used against potential side-effects that might occur following PRRNT
8. Describe the expected results/benefits of the PRRNT
9. Discuss the expected duration of the response to PRRNT
10. Discuss number of PRRNT treatment cycles and the duration of interval between the cycles
11. Describe the treatment protocol of an individual cycle
12. Describe the expected total duration of the treatment
13. Circumstances leading to the interruption of discontinuation of the treatment; both by the physician or the patient.
14. A description of post-therapy recommendations and a list of laboratory testing, following each cycle
15. A description laboratory tests and imaging procedures to be performed (recommended) after completing the last cycle
16. Provide contact information of the person/s to whom questions to be addressed regarding the PRRNT
17. Were appropriate, an acknowledgment that the treatment may involve currently unknown risks to a patient or the fetus of a patient who become pregnant.
SAMPLE OF A CONSENT FORM

This sample contains major information that shall be provided in writing or communicated orally in a simple and comprehensible language to the patients and or their guardian/s. Please note that the sample provided herein should **only** be used as a reference as local requirements, regulations or procedures may vary among institutions. Hence the final consent should express those particular local requirements.

**Informed Consent and Authorization form for patients with neuroendocrine tumours receiving Peptide Receptor Radionuclide Therapy (PRRNT)**

[Insert Name and Address of Hospital]
Place and Date

Dear Madam/Sir,

Your physician/multidisciplinary team have suggested you to undergo a PRRNT and may have informed in broad lines about the treatment. In order for you to better decide whether you wish to undergo this treatment (PRRNT) you will receive in addition to our conversation detailed printed information sheet for you to read at your own pace. This should also allow you to discuss its content with others. At any time, you may ask for additional information from the doctors listed at the end of this form.

**Your current medical situation**

From prior discussions, it is clear that you suffer from a malignant disease that cannot be cured by surgery and/or that does not respond previous medical treatments. One of the novel forms of treatment for your disease is termed Peptide Receptor Radionuclide Therapy (PRRNT). Recently you have had a scan in the department of Nuclear Medicine. This scan determined that the malignant cells in your body are capable of binding a carrier-peptide which is linked to a radioactive substance. Because of this, the disease can be irradiated from inside. The intention of this treatment is to reach all malignant cells in the body without affecting any normal tissue.

**Aims of the treatment**

The aims of this treatment in patients with neuroendocrine tumours are:
1. to reduce/abolish signs/symptoms caused by the disease
2. to accomplish tumour shrinkage reducing the size and number of tumour sites
3. to enable a combination with complementary forms of treatment such as embolization or further surgical resection.

**Treatment principles (how the treatment works)**

Peptide Receptor Radionuclide Therapy (PRRNT) is a treatment procedure delivered by nuclear medicine to treat somatostatin receptor-positive malignant tumours. For PRRNT, we use short-range beta-emitting radioisotopes either Yttrium-90 (Y-90) or Lutetium-177 (Lu-177) to irradiate the cancer. For this purpose the radioisotopes is attached to a molecule (peptide) similar to the one used for your diagnostic Nuclear Medicine investigation (scintigraphy) that you have undergone and showed that the (PRRNT) treatment can be...
effective in your case. It showed that the therapeutic (the radiopeptide) binds effectively to the malignant cells to allow their irradiated from within.

Much experience has been acquired with this type of treatment in patients with neuroendocrine tumours over the past years. Since mid 90’s, many patients in different institutions worldwide have been treated. The published results, to date, are encouraging. Durable relief of symptoms and stopping the growth of the tumour (stabilization of disease progression) are reported in over 70% of the patients. Reducing the size of the cancer (Tumour shrinkage) was reported up to 30%.

Procedure (how the treatment is done)
On the day of the therapy, following your admission in the Nuclear Medicine ward, an intravenous line will be placed in your forearm. An anti-emetic to prevent vomiting is then administered. You will receive additional infusion one containing saline and another with an amino-acids mixture. Your vital signs will be monitored by measuring blood pressure, pulse rate and your well being. The aim of the amino-acid infusion is to protect the kidney and reduce its radiation by the radiopharmaceutical. The other salt fluid is given to make sure that you have sufficient fluid in your body to produce a lot of urine. The administration of the radioactive peptide begins 30 min following the start of the amino acid infusion and lasts for 5-30 min. The amino-acids infusion will continue throughout 4-5 hours.

In the following days, part of the activity will leave your body through the urine. The level of radioactivity in your body will be monitored until it has reached safe levels to permit your discharge home. In most cases you will be discharged within 24 to 48 hours.

During the first week after therapy, several measurements using the SPECT camera will be performed to determine the body distribution of the radio-peptide. This will allow assessing the irradiation of the kidneys and of the cancer tissue. This latter procedure is termed “dosimetry”.

Following the first cycle and in between subsequent PRRNT treatment cycles, your blood will be monitored for changes in white blood cell counts, platelet counts and kidney function. These blood tests should be performed four weeks after a treatment cycle and two to four weeks before the next cycle.

Potential risks and discomforts
The most frequent side-effects are a transient decrease in the number of white blood cells and blood platelets. This decrease is usually mild and temporary. In only few cases the platelets might drop to dangerous levels, which may require treatment and could lead to postponing the next treatment cycle. As blood platelets assist in the clotting of blood, a decrease in platelet concentration might increase the risk of internal bleedings. A decrease in white blood cell count may result in infections. An increased frequency of infections or bleedings was not observed in the patients receiving PRRNT. Other side effects that occur more frequently are fatigue, nausea (30%) and vomiting (15%) usually on the first day. Hair loss (not baldness) is observed in about 65% of the patients receiving PRRNT. However, your hair will resume growing when the treatment is concluded.

On the longer run more serious and feared side-effects occurred only in a few patients. The Myelodysplastic Syndrome (MDS) is a pre-stage of leukemia, can occur in up to 3 patients out of 500 receiving this treatment.
In 2 patients, a serious deterioration of kidney function occurred. In one patient, renal insufficiency developed one year after the last treatment. This patient already had periods of unexplained decreased kidney function in the year preceding the therapy. It is therefore not certain whether the therapy was the cause of the further deterioration of the kidney function. In the other patient, a serious deterioration of kidney function occurred 3 1/4 years after the last therapy. In part this was also caused by the medication that the patient took.

Lastly, in 3 patients with very extensive, diffuse liver metastases, a deterioration of liver functions occurred in the weeks following the therapy. In 2 patients this was temporary, whereas the other patient died shortly after.

**Known Risks, Side Effects and Discomforts of the PRRNT**

During the therapy cycles, the patient is at risk of experiencing some or all the side effects listed below. These conditions should be discussed with your attending physician based on your individual risk profile. The known side effects can vary from person to person. Many side effects disappear after a short time; however, some side effects may be serious and have longer lasting and/or permanent effects on the body. Please be advised that such side effects could indirectly be fatal.

**Short-term (commonly observed) side effects**

You may experience side-effects. Not all side-effects will occur in all patients. If you have unexplained signs or symptoms we ask you to contact your referring physician.

1. PRRNT may cause nausea, vomiting, diarrhea, and indigestion to occur immediately during or after therapy. These symptoms largely remit following the cessation of the amino-acid infusion.
2. Allergic reactions (itchy rash, anaphylaxis) may also occur following the kidney protection infusion with a plasma expander like Gelatin, (Gelafusin or any other, a plasma expander) during therapy administration.
3. Carcinoid Crisis - If your cancer is functionally active, you may experience a so called carcinoid crisis during or following therapy. This is due to a sudden release of hormones from the cancer cells into the bloodstream. This can cause circulatory and breathing difficulties, accompanied by headache and some other neurological symptoms. When this occurs it is treated vigorously and sometimes requires treating you with short-acting somatostatin medication.

**Medium-term (commonly observed) side effects**

1. Transient decrease in red blood cells (erythrocytes), white blood cells (leucocytes/lymphocytes)
2. Transient decrease of platelets (thrombocytes)

**Long-term (rarely observed) side effects**

1. Repeated administration of PRRNT may result in serious deterioration of renal function in less than 1% of the cases
2. MDS (myelodysplastic syndrome) has been observed in less than 1% of patients and may be associated with prior chemotherapy.
3. Other unknown deleterious effects may occur that have not been observed to date

**Pregnancy and Breast Feeding**

Pregnant women are forbidden by law to undergo this treatment. Breast-feeding must be withheld during the whole period of therapy. Women in reproductive age should take precautions so as not become pregnant during the trial or within 6 months after the last treatment.

If applicable, your attending physician can discuss the most suitable method of contraception. If, despite all precautions, you do get pregnant during the trial period, please contact your attending physician immediately. The potential hazard of this treatment to your unborn child is not known.

**Post-therapy Monitoring**

To evaluate the results and the effects of the treatment additional investigations and tests are necessary. The results of the treatment are evaluated by means of blood tests, urine tests, radiological procedures (usually CT or MRI scans), and if necessary, additional tests. Following the last therapy cycle, your attending physician will continue to monitor the course of your disease. In this respect, it is important to register any side-effects and their severity to your attending physician.

**Privacy and confidentiality declaration**

All the data and outcomes related to your treatment will treated as confidential by the physicians and staff responsible for this therapy. Treatment data that can only be consulted by the treating team or by a sanction committee that oversees ethical conduct of care. The treatment data will be handled in accordance with the law on the protection of personal data and the privacy regulations of Institution or country (if applicable).

We wish to store your data in order to possibly perform further evaluations for publication purposes. If you do not agree, we will of course respect you wish. You need to confirm your refusal by signing below. If you do agree please confirm below as well.

I do agree ___________ I do NOT agree ___________ date: ___________

**Refusal and discontinuation during the treatment**

You can stop your treatment at any time point without further explanation. You are free to withdraw your consent by informing your physician. Refusal to continue will not affect further medical management.

**Further information/inquiries**

If you have any questions about the treatment, whether before or during the cycles, you may contact your attending physician or one of the physicians at the department of Nuclear Medicine listed below:
Institutions name
Dept. of NM: Phone: xxx-yyyyyyyy

Responsible physicians:
name Phone: xxx-yyyyyyyy E-mail aaa@bbbbbbbb.com
name Phone: xxx-yyyyyyyy E-mail aaa@bbbbbbbb.com

We ask you to sign and date the attached consent form in the presence of the responsible physician for the therapy.

**AUTHORIZATION FORM TO RECEIVE TREATMENT with ........ (insert the radiopharmaceutical)**

I confirm that I have read the information form for the patients. I understand the information. I had the opportunity to ask additional questions. These questions have been answered to my satisfaction. I had sufficient time to think about the proposed treatment. I know that my decision is voluntary and that I can withdraw my consent at any time without any need to explain why I do so.
I give permission to inform my general practitioner and/or attending physician about my decision of being treated with PRRNT.
I give permission to use the data for the aims that were described above and agreed upon.
I give permission to be treated with PRRNT according to the information provided above.

Patient Name (Print) Signature: Date:

__________________ ______________ __________

Responsible Physician Signature: Date:

__________________ ______________ __________
ABBREVIATIONS

5-HIAA  5-Hydroxyindoleacetic acid  
ACTH  Adrenocorticotropic hormone  
APUD  Amin precursor uptake and decarboxylation  
BED  Biological effective dose  
Bq  Becquerel (one nuclear disintegration per second)  
Cg-A  Chromogranin A  
CEA  Carcino-Embryonic antigen  
Ci  Curie  
CT  Computed tomography  
DOTA Ga-68  Ga 68-labelled 1,4,7,10-tetraazacyclododecane-N,N',N,N'-tetraacetic acid used with PET  
DOTA-TOC  DOTA-d-Phe(1)-Tyr(3)-octreotide  
DOTA- NOC  Somatostatin analogue 1-Nal3-octreotide (NOC) attached to Ga-68 DOTA has high affinity to sstr-1, 2 and 5 subtypes  
DTPA  Diethylene triamine pentaacetic acid  
ECG  Electrocardiogram  
EDTA  Ethylene diamine tetraacetic acid  
ELISA  Enzyme-linked Immunosorbent Assay  
ENETS  European Neuroendocrine Tumour Society  
Er  Erbium  
FNA  Fine needle aspiration  
GEP  Gastroenteropancreatic peptide  
Ga  Gallium  
GFR  Glomerular filtration rate  
Gy  Gray, one joule of ionizing radiation absorbed by one kilogram of tissue  
I  Iodine  

Final draft submitted for external revisor  
J.J. Zaknun, IAEA
In  Indium
HPF  High power field magnification
HPLC  High pressure liquid chromatography
Ki-67  Immunohistochemical staining to assess cellular proliferation using Ki-67 monoclonal antibody
Lu  Lutetium
MAG3  Mercaptoacetyltrimglycine
MEN-1  Multiple Endocrine Neoplasia syndrome type 1
MEN-2  Multiple Endocrine Neoplasia syndrome type 2
Mo  Molybdenum
MRI  Magnetic resonance Imaging
MTC  Medullary thyroid cancer
NaI  Sodium iodide
NET/s  Neuroendocrine tumour/s
NM  Nuclear medicine
Octreotide  An Octapeptide that mimics the action of the natural occurring somatostatin
PET  Positron emission tomography
pH  Potential of hydrogen
PP  Pancreatic peptide
PRRNT  Peptide receptor radionuclide therapy
QA  Quality Assurance
QC  Quality Control
Re  Rhenium
RIA  Radioimmunoassay
SEER  “Surveillance, Epidemiology and End Results” database
Sm  Samarium
Somatostatin  Growth hormone inhibiting hormone, interacts with cell signalling via the G-protein coupled somatostatin receptor/s
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>SPECT-CT</td>
<td>Single photon emission computed tomography-computed tomography</td>
</tr>
<tr>
<td>Sstr</td>
<td>Somatostatin receptor, subtypes 1, 2, 3, 4 and 5 are known.</td>
</tr>
<tr>
<td>Sr</td>
<td>Strontium</td>
</tr>
<tr>
<td>Sv</td>
<td>Sievert</td>
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<tr>
<td>Tc</td>
<td>Technetium</td>
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<tr>
<td>UICC</td>
<td>Union International Contre le Cancer</td>
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<tr>
<td>VHL</td>
<td>Von Hippel-Lindau syndrome</td>
</tr>
<tr>
<td>VIP</td>
<td>Vasocative Intestinal Peptide</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>Y</td>
<td>Yttrium</td>
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</tbody>
</table>
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