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PROTOCOL PENTRU DIAGNOSTICUL TUMORILOR NEUROENDOCRINE

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Neuroendocrine Tumors (NET) 10

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Abstract

The neuroendocrine tumors represent a challenge both for diagnosis and treatment involving many specialists during the positive diagnosis, staging and therapy response evaluation. Over the past decades, nuclear medicine procedures have acquired a relevant role in the detection of neuroendocrine tumors (NET). This chapter describes an overview of these tumors, presents the classification and the main indications of nuclear medicine tests. The recent introduction of specific PET tracers for NET studies increased even more the nuclear diagnosis and therapeutic interest in this pathology. This chapter details the procedure with In-111 DTPA octreotide and presents clinical cases.

"As the area of light expands, so does the perimeter of darkness"

A. Einstein

10.1 Overview

Neuroendocrine malignant tumors (NET), defined as epithelial neoplasms with predominant neuroendocrine differentiation, arise in most organs of the body. Some of the clinical and pathologic features of these tumors are characteristic of the organ of origin, but other attributes are shared by neuroendocrine neoplasms irrespective of their anatomic site. The multidisciplinary consensus group of experts (North American Neuroendocrine Tumours Society – NANETS, the College of American Pathologists – CAP, the European Neuroendocrine Tumours Society – ENETS) in the field of NET has recommended a minimum pathology data set of features to be included in pathology reports. The system of classification and nomenclature is depending on the site of the tumor and also of the differentiation grade.

10.1.1 Systems of Nomenclature and Grading System for Neuroendocrine Tumors

10.1.1.1 Lung and Thymus NET (WHO)

Grade of differentiation

- Low grade:
  - Carcinoid tumors
  - <2 mitoses/10 hpf (high power filed) and no necrosis
- Intermediate grade:
  - Atypical carcinoid tumors
  - 2–10 mitoses/10 hpf or foci of necrosis
- High grade:

D. Piciu, *Nuclear Endocrinology*,
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- Small cell carcinoma
- Large cell neuroendocrine carcinoma
- >10 mitoses/10 hpf

10.1.1.2 Gastroenteropancreatic (GEP) NET (WHO 2010, ESMO 2012)

Grade of differentiation

- WHO 1-Low grade:
  - Neuroendocrine neoplasm, grade 1
  - <2 mitoses/10 hpf and <3% Ki 67 index
- WHO 2-Intermediate grade:
  - Neuroendocrine neoplasm, grade 2
  - 2–20 mitoses/10 hpf and 3–20% Ki 67 index
- WHO 3-High grade:
  - Neuroendocrine carcinoma, grade 3, small cell carcinoma
  - Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma
  - >20 mitoses/10 hpf and >20% Ki 67 index
  - mixed adenocarcinoma and neuroendocrine tumor
  - tumor like lesions

Functionally active tumors:

- Functionally active NET present with clinical symptoms because of excessive hormone release from the tumor cell.
- Examples of such events are:
  - Gastrinoma, excessive gastrin production, Zollinger–Ellison syndrome
  - Insulinoma, excessive insulin production, hypoglycemia syndrome
  - Glucagonoma, excessive glucagons production, glucagonoma syndrome
  - VIPoma, excessive production of vasoactive intestinal peptide (VIP), Watery diarrhea, hypokalemia–achlorhydria syndrome
  - PPoma, excessive PP production, (generally classified as nonfunctioning PETs)
  - Somatostatinoma, excessive somatostatin production
  - CRHoma, excessive corticotropin-releasing hormones production
  - Calcitoninoma, excessive calcitonin production
  - GHRHoma, excessive growth hormone-releasing hormone production
  - Neurotensinoma, excessive neurotensin production
  - ACTHoma, excessive production of adrenocorticotropic hormone
  - GRFoma, excessive production of growth hormone-releasing factor
  - Parathyroid hormone-related peptide tumor

Functionally inactive tumors:

- Functionally inactive NET are diagnosed in several ways:
  - During routine US performed for the investigation of unexplained upper abdominal complaints
  - In the case of large tumors of the pancreatic head because of the consequent extrahepatic jaundice
  - In the case of patients with relapsing abdominal cramps, as a result of intestinal pseudo-obstruction by a functionally inactive NET of the lower jejunum and ileum
  - As a result of tumor mass symptoms

Genetics:

- Non-sporadic NET arise as a result of syndromes caused by an autosomal dominant mutation

Symptoms:

- Insulinoma: hypoglycemia
- Gastrinoma: peptic ulcer disease
- VIPoma: diarrhea
- Glucagonoma: necrotic skin rush
- Somatostatinoma: mass effect
- Carcinoid: flush, rush, diarrhea, sweat
- Non-functional: mass effects

10.2 Nuclear Imaging of Neuroendocrine Tumors (NET)

Imaging studies for NET are generally performed for an initial evaluation of the extent of the disease and subsequent follow-up. The goals for the initial evaluation include the identification of the primary tumor, staging and treatment planning. Subsequent follow-up imaging studies are performed for the surveillance after complete resection or during periods of stability and evaluation of response after the treatment.

Imaging modality commonly used includes the following:

- Small-bowel series
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- (In-111 DTPA) octreotide scintigraphy – Octreoscan
- Metaiodobenzylguanidine (MIBG) scintigraphy
- Positron emission tomography (PET) and PET/CT

Imaging studies generally recommended at the time of the initial evaluation include plane film radiography of the chest, cross-sectional imaging (CT or MRI) of the abdomen and pelvis and Octreoscan scintigraphy.

Among patients undergoing surveillance after complete resection, a chest radiography and periodic (every 6–12 months) cross-sectional imaging of the abdomen and pelvis is recommended. For patients having an advanced disease, it is important to evaluate if peptide receptor radiotherapy (PRRT) represents a good treatment option.

In-111- and Tc-99m tektrotyd labeled somatostatin analogues were developed for the scintigraphy of NET. It shares the receptor-binding profile of octreotide, which makes it a good radiopharmaceutical for imaging of somatostatin receptors 2 and 5.

Imaging is generally performed at 4–6 h and at 24 h. Imaging at 24 or even 48 h provides better contrast because of lower background activity. However, there is often physiological bowel activity that may produce false-positive results. SPECT/CT may be helpful in resolving the nature of indeterminate lesions found on CT and enhances the sensitivity and specificity of the study.

The scintigraphy can be performed for patients on long-acting octreotide but is best performed at the end of the dosing interval (3–6 weeks after the last dose).

For patients on octreotide delivered via a continuous-infusion pump or those who received intermittent short-acting octreotide for rescue, it is recommended that these be stopped 48 h before and during testing if possible.

The In-111 octreotide scintigraphy is performed to evaluate the feasibility of PRRT as

a scan with intense uptake at all known sites of disease, and it is associated with a higher response rate after radiotherapy with somatostatin receptor targeting.

I-123-MIBG molecular imaging has also been used for NET but have the greatest efficacy in patients with pheochromocytoma, paraganglioma or neuroblastoma. Some tumors, negative on In-111 octreotide scintigraphy, can be better seen with I-123-MIBG.

Positron emission tomography F-18-fluorodeoxyglucose (FDG) imaging, although successful for many solid tumors, has generally not provided additional information about the extent of the disease for well-differentiated NET because of their generally lower proliferative activity.

F-18 FDG PET imaging may be used to characterize tumor aggressiveness with higher FDG uptake (expressed as SUV values) having a worse prognosis. This may be helpful when the tumor seems more aggressive than the histology indicates, and additional information for FDG imaging may result in changes of treatment.

Prior studies have shown C11-5-hydroxytryptophan (HTP) PET to be a promising imaging modality for the detection of NET. The serotonin precursor 5-HTP labeled with C-11 was used and showed an increased uptake and irreversible trapping of this tracer in NET. Other new PET imaging agents for NET include F-18-DOPA, Ga-68-DOTA-TOC, Ga-68-DOTA-NOC and F-18-PGluc-TOCA. In addition, Tc-99m-depreotide, which has a greater affinity to somatostatin receptor 3, has also been used for tumor imaging. Although these novel imaging techniques are promising, clinical experiences are limited.

As the latest ESMO guidelines (2012) recommend follow-up investigations should include biochemical parameters and conventional imaging. In patients with R0/R1 resected NET G1/G2, it is recommended that imaging is performed every 3–6 months (CT or MRI), and in NEC G3, every 2–3 months. Somatostatin receptor imaging, either Octreoscan or PET/CT using Ga-68-DOTA-TOC/-NOC/-TATE should be included in the follow-up and is recommended after 18–24 months if expression of somatostatin receptor 2A has been proven on the tumor cells. In the case of rapid tumor progression or if imaging information is lacking, it may be necessary to re-biopsy liver metastases to re-assess the proliferative activity.

Name of examination

10.2.1 NET Imaging with In-111 Octreoscan

Radiopharmaceutical:

- In-111 pentetreotide (Octreoscan)

Principle:

- Octreoscan is a radiolabeled analogue of somatostatin indicated for the scintigraphic localization of neuroendocrine tumors bearing somatostatin receptors.

Technique:

- Patient preparation:
  - Bowel preparation, especially for abdominal suspected lesions
  - Hydration and frequently voiding of the urinary bladder
  - Attention to diabetic patients where may cause paradoxical hypoglycemia
  - Temporarily withdrawal of octreotide therapy
  - Attention to breastfeeding and childbearing age patients (see chapter of Radioprotection)

- Dose: 3–6 mCi (111–220 MBq)/patient
- Injected I.V.
- It is necessary to wait 4–6 h after the injection for the first images. Delay images may be registered at 24 h or 48–72 h.
- Patient position: supine
- Gamma camera
  - Medium-energy general purpose (MEGP) collimator
- Acquisition:
  - The gamma camera is positioning anteriorly and next posteriorly or simultaneous in dual head camera.
  - Photon peaks at 172 and 245 keV and 20% windows.
  - 256 × 256 matrix or in whole body 256x1024
  - Min 500,000 counts/image.
  - WBS speed 3 cm/min.
  - Also, spot images on the region of interest and lateral views of head/neck, chest and abdomen may be obtained.
  - SPECT is usually recorded with 60 projections of 6° each; or 90 projections of 4° each. Matrix 64 × 64.
  - 45–60 s/projection.
- Processing: There are special PC programs for image processing; additional analysis of counts in different region of interest (ROI) may be used.

Clinical applications:
- Diagnosis and management of receptor bearing gastro-entero-pancreatic (GEP) neuroendocrine tumors and carcinoid tumors; other non-GEP neuroendocrine tumors.
- Diagnosis of carcinoid; islet cell carcinoma; gastrinoma; glucagonoma; insulinoma; VIPoma; motilinoma.

Necessary additional examinations:
- CT, MRI
- Ultrasound
- Serologic tests of specific tumor markers
- Fine needle aspiration biopsy (FNAB)
- PET/CT with specific tracers

Comments:
- If there is no uptake of Octreoscan, the use of somatostatin analogues in the treatment is discouraged.
- SPECT/CT will add superior detection

Reports:
- The report will include a description of the normal distribution and pathologic uptakes; the report should mention the correlation of nuclear findings with the morphological images.

10.2.2 NET Imaging with Tc-99m Tektrotyd

Radiopharmaceutical:

- Tc-99m Tektrotyd is a radiopharmaceutical indicated for diagnostics of pathological lesions in which somatostatin receptors are overexpressed (particularly subtype 2 and, to a lesser extent, subtypes 3 and 5) and which may be imaged by the labelled ligand.

Principle:

- Octreoscan is a radiolabeled analogue of somatostatin indicated for the scintigraphic localization of neuroendocrine tumors bearing somatostatin receptors.

Technique:

- Patient preparation:
  - Unless there are indications for other method of the patient preparation, the patient is recommended to stay on light diet one day before examination. On the day of examination, the patient should fast until the end of the acquisition. If there is a need for examination after 24 hours, it is recommended that a mild laxative be given to the patient starting the evening before. Method of patient preparation may depend on the applied examination protocol and the localization of imaged lesions. However, optimal imaging of abdominal cavity is obtained after the application of liquid diet 2 days before the examination and after administration of laxatives on the day before the examination.
  - Attention to breastfeeding and childbearing age patients (see chapter of Radioprotection)
- Dose: 370 to 925 MBq.
- Tc-99mTektrotyd is administered intravenously in a single dose after labelling of the kit using a sterile, oxidant-free sodium pertechnetate solution for injection. Technetium-99m in 1 ml of eluate of sodium pertechnetate-Tc-99m solution for injection with activity of 740 MBq - 1200 MBq (maximally 2200 MBq) may be used for labelling of one kit. This activity is sufficient for examinations of 1 – 2 adults. Radioactivity of administered dose should be always adjusted with respect to its diagnostic usefulness. The solution may be additionally diluted for more convenient administration.
- Patient position: supine
- Gamma camera
  - Low energy high resolution (LEHR) collimator
- Acquisition:
- Acquisition should be carried out between 2 – 4 hours after intravenous administration of the preparation. The examination may be complemented by acquisition after 10 minutes, 1 hour and 24 hours after administration of the preparation. It is recommended to carry out the examinations using Whole Body technique and SPECT of selected body areas. The gamma camera is positioning anteriorly and next posteriorly or simultaneous in dual head camera.
- Photon peaks at 172 and 245 keV and 20% windows; WBS speed 3 cm/min.
- Also, spot images on the region of interest and lateral views of head/neck, chest and abdomen may be obtained.
- SPECT is usually recorded with 60 projections of 6° each; or 90 projections of 4° each. Matrix 64 × 64.
- SPECT/CT should be applied whenever is possible for better resolution and sensitivity

Processing: There are special PC programs for image processing; additional analysis of counts in different region of interest (ROI) may be used.

Clinical applications:

- Gastro-entero-pancreatic neuroendocrine tumours (GEP-NET);
- Pituitary adenomas;
- Tumours originating in a sympathetic system;
- Pheochromocytoma, paraganglioma, neuroblastoma, ganglioneurinoma etc.;
- Medullary thyroid carcinoma;
- The preparation may be potentially useful in the case of other tumours expressing somatostatin receptors of various intensity.
- Other tumours which may overexpress somatostatin receptors: breast cancer, melanoma, lymphomas, prostate cancer, NSCLC, sarcoma, renal cell carcinoma, differentiated thyroid carcinoma, astrocytoma according to WHO I-IV (including glioblastoma multiform G-M), meningioma, ovarian cancer.

Necessary additional examinations:

- CT, MRI
- Ultrasound
- Serologic tests of specific tumor markers
- Fine needle aspiration biopsy (FNAB)
- PET/CT with specific tracers

Comments:

If there is no uptake of Tc-99m Tektrotyd, the use of somatostatin analogues in the treatment is discouraged.

The studies published in the latest years, showed comparable results with octreoscan in NET detection, but with lower irradiation, better dosimetry and larger availability.

Reports:

The report will include a description of the normal distribution and pathologic uptakes; the report should mention the correlation of nuclear findings with the morphological images.

A synthetic presentation of diagnosis in NET is presented in Fig. 10.1, adapted from Bodei L, 2015.

Fig. 10.1 Diagnosis methods used in neuroendocrine tumors, adapted from Bodei L, 2015

10.3 Nuclear Therapy of Neuroendocrine Tumors

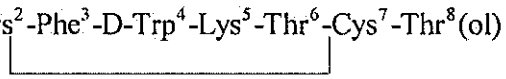
The primary treatment of neuroendocrine tumors (NET), such as the carcinoid, is surgery with curative intent or with the intent to debulk the tumor mass. In 80% of patients with NET for whom this is impossible, alternatives such as external beam radiation therapy or chemotherapy are suboptimal because these well-differentiated tumors are relatively unresponsive. Most of these tumors express somatostatin receptors, especially subtype 2, in high abundance, which very rapidly bind and internalize targeted peptides. Somatostatin analogues, such as octreotide, can be used to treat carcinoid syndrome, and recent studies have also demonstrated substantial effects on tumor growth characteristics

and modest prolongation of survival.

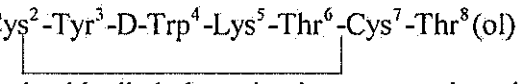
The rationale for using radiolabeled somatostatin analogues is based upon the evidence that they rapidly accumulate in the up-regulated overexpressed somatostatin receptor-containing tumors. Somatostatin peptide analogues, coupled with a complexing moiety (DOTA) can be labeled with the beta-emitters Y-90 or Lu-177. By targeting somatostatin receptor-positive tumors, they may deliver a tumouricidal radiation dose, and regression has been demonstrated after therapy with radiolabeled somatostatin analogues.

Somatostatin acts through interaction with receptors expressed on the surface of cells (in both normal and malignant tissues), named as somatostatin receptors. Six subtypes have been characterized and named somatostatin receptor subtype 1-5 (SSTR1, 2A, 2B,3,4 and 5).

The **octreotide** is a somatostatin analogue with the structure:



Researchers found that if Phe^3 is substituted with Tyr^3 it is possible to labeled with radioiodine isotopes, both for diagnostic and for therapy.



Octreotide was derivatized with diethylenetriaminepentaacetic acid (DTPA) on the amine terminus. Attaching this chelate to the peptide allowed radiolabelling of the molecule with In-111.

Following that step, with the aim to find the best agent for PRRT, the chelating agent, DTPA, (coupled to octreotide) was substituted with DOTA (tetra-aza-cyclo-dodecane-tetraacetic acid), which enabled the radiolabelling of this conjugate with Y-90, Lu-177 or other radionuclides.

DOTATOC: DOTA-Phe^1-Tyr^3-Octreotide

DOTANOC: DOTA-Nal^3-Octreotide (DOTA- Naphythyl-alanine conjugate with octreotide)

Octreotate is another peptide analogue of somatostatin, which differs from octreotide where the C-terminal amino acid residue is threonine (instead of threoninol in octreotide)

DOTATATE: DOTA-Thy^3-$Thre^8$-Octreotide (Octreotate)

Lu-177 is a medium-energy beta-emitter with a maximum tissue penetration of 1.6 mm and a physical half-life of 6.7 days. It also emits medium- and low-energy gamma radiation, which can be used for quantitative imaging and dosimetry. Binding of Lu-177 octreotate in NET expressing somatostatin receptor subtype-2 is nine times higher than that of the standard diagnostic imaging agent In-111 octreotide and seven times higher than that of the therapeutic agent Y-90 octreotide.

Tumor-targeted radiopeptide therapy is under investigational and clinical evaluation in European and Australian centers. Initial results with In-111 octreotide were disappointing, but more promising results were achieved with Y-90 octreotide and more recently with Lu-177 octreotate and Y-90 octreotate. Treatment of NET with Lu-177 octreotate results in impressive control of NET progression in a high percentage of patients, with little toxicity. However, virtually no malignancies have been cured using single-modality treatments. Multimodality treatment is required to control metastatic

cancer. The synergistic combination of chemotherapy and radionuclides has the potential to enhance efficacy and minimize toxicity.

Radiation therapy of cancer, when combined with chemotherapy using either 5-fluorouracil (5-FU) or its prodrug capecitabine, has improved survival rates for a variety of tumor types when compared with radiation therapy alone.

Since the last edition of the book, in 2011, the progresses in this field were considerable. One of the most experimented scientist in peptide receptor radionuclide therapy (PRRT) is Lisa Bodei who published in 2016: "PRRT has been utilized for more than two decades and has been accepted as an effective therapeutic modality in the treatment of inoperable or metastatic gastroenteropancreatic neuroendocrine neoplasms (NENs) or neuroendocrine tumors (NETs). The two most commonly used radiopeptides for PRRT, Y-90-octreotide and Lu-177-octreotate, produce disease-control rates of 68%-94%, with progression-free survival rates that compare favorably with chemotherapy, somatostatin analogues, and newer targeted therapies. In addition, biochemical and symptomatic responses are commonly observed. In general, PRRT is well tolerated with only low to moderate toxicity in most individuals".

Recently more clinical trials and strategies are developed including combinations with targeted therapies or chemotherapy, intra-arterial PRRT, and salvage treatments. Sophisticated molecular tools need to be incorporated into the management strategy to more effectively define therapeutic efficacy and for an early identification of adverse events. The strategy of randomized controlled trials is a key issue to standardize the treatment and establish the position of PRRT in the therapeutic algorithm of NENs.

10.3.1 Treatment Proposed Plan

- Lu-177 octreotate.
- Each patient receives an infusion of amino acids comprising 11.6 g/L lysine and 23 g/L arginine, at 250 mL/h for 4 h.
- At 30 min, 7.8 GBq [Lu-177-DOTA,Tyr^3] octreotate must be co-infused with the amino acids via a side-line over 10 min.
- Routine antiemetic therapy is given in the form of intravenous and oral 2 mg lorazepam.
- Chemotherapy with oral 1.650 mg/m^2 capecitabine for 14 consecutive days was started on the morning of the radionuclide therapy.
- Cycles of capecitabine were repeated every 8 weeks at the time of each subsequent radiopeptide infusion.

A key concept emerging from targeted therapies is the recognition of the clinical importance of tumor stabilization in progressive malignancy.

10.3.2 Radiometabolic Therapeutic Approaches

In 2008, Modlin et al. reviewed the past decade of literature on neuroendocrine tumor treatment and summarized current therapeutic options. They remarked that the majority of tumors are diagnosed at a stage when radical surgical intervention, the only curative treatment, is no longer an option. Biotherapy with somatostatin analogues is currently the most efficient source of palliation. There may be a role for interferon agents in selected individuals, but substantial adverse events often limit their use. Conventional

chemotherapy has minimal efficacy but may be of some use in undifferentiated or highly proliferating neuroendocrine carcinomas and pancreatic neuroendocrine tumors. Hepatic metastases, depending on size, location and number, may be amenable to surgical resection, embolization or radiofrequency ablation. PRRT (peptide receptor radionuclide therapy) may reduce tumor size but in most circumstances has a tumor-stabilizing effect. Although various anti-angiogenesis and growth factor–targeted agents have been evaluated, so far they fall short of expectations.

The somatostatin receptors, which are overexpressed in a majority of neuroendocrine tumors, are the first and best example of targets for radiopeptide-based imaging and radionuclide therapy.

The somatostatin analogue In-111 octreotide allows the localization and staging of neuroendocrine tumors that express the appropriate somatostatin receptors. Newer modified somatostatin analogues, including Tyr3 octreotide and Tyr3 octreotate, are successfully being used in tumor imaging and radionuclide therapy. Because there are few effective therapies for patients with inoperable or metastatic neuroendocrine tumors, this therapy emerges as a promising and novel option for these patients.

Forrer et al. stress the essential role of adequate dosimetry in effective and safe PRRT. Besides the kidneys, the bone marrow is a potentially dose-limiting organ. The radiation dose to the bone marrow is usually calculated using the MIRD model, according to which the accumulated radioactivity of the radiopharmaceutical in the bone marrow is worked out from that recorded in the blood.

The treatment of metastatic neuroendocrine tumors depends on the aggressiveness of the disease. Early diagnosis of metastatic spread of neuroendocrine tumors is hugely important, as the detection of distant metastases has a major impact on treatment choices. To date, however, no standard procedure was established for the early diagnosis of bone metastases from neuroendocrine tumors.

At present, there is a research interest in finding the best somatostatin (SST) analogue having the capability to link to all five isolated and characterized somatostatin receptors 1,2,3,4,5 (SSTR1-5). In this way, it could be possible to increase the diagnostic sensitivity also in NET not expressing SSTR2 and SSTR5 (which are the main targets for octreotide), such as in insulinoma. As an alternative, a wider sensitivity can be achieved using other neuropeptides such as bombesin, vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase–activating polypeptide (PACAP), cholecystokinin (CCK), gastrin-releasing peptide (GRP), gastrin, neurotensin, neuropeptide Y (NPY), substance P, oxytocin, luteinizing hormone–releasing hormone (LH-RH), glucagon-like peptide 1 (GLP-1), calcitonin, endothelin, atrial natriuretic factor and alpha-melanocyte-stimulating hormone (α-MSH).

Being at present more easily available and cheaper, DOTA peptides can be considered the first choice in NET, except for tumors not presenting a favorable SSTR expression, such as insulinoma. A wider experimental demonstration of a similar behavior between F-DOPA and I-131-MIBG could create an interesting perspective for the utilization of F-DOPA as a priori tracer for the therapeutic efficacy in patients with NET.

In general, since its first implementation by the Rotterdam group in 1994, only a few peer-reviewed papers have been published on PRRT in a larger cohort of patients over the last 15 years, even if there is an important number of abstracts, textbook articles as well as review articles on PRRT by various groups that have been published worldwide

over the last years.

Today, Y-90 and Lu-177 are the two radionuclides used for PRRT with SST analogues. In-111 pentetreotide was first pioneered for PRRT but was subsequently displaced by radiolabeled DOTA-TOC and DOTA-TATE derivates. This is due to the fact that In-111-labeled peptides are not ideal for PRRT because of the small particle range and thus a short tissue penetration.

The ENET Consensus Guidelines for the Standards of Care in NET tried to define the minimum requirements for patients eligible for PRRT, based on the fact that at the different centers, different SST analogues are being used, and their availability depends on national law and local permissions. Among these criteria, high uptake by the tumor lesions, inoperable disease, a Karnofsky score of >50% and a life expectancy of at least 3–6 months are required. Contraindications are an impaired renal function (i.e., a creatinine clearance of <40–50 mL/min), an impaired hematological function and severe hepatic and cardiac impairment.

In patients relapsing after PRRT with Y-90-DOTA-TOC, the Lu-177-labeled DOTA-TOC may be an alternative further treatment option that also was proven to be clinically safe and efficacious.

10.3.3 Combination Treatments

Long-acting octreotide (30 mg intramuscular every 4 weeks) has recently been shown to inhibit tumor progression in patients with metastasized well-differentiated midgut NET and may therefore have a potential role in the concomitant treatment of these patients.

Furthermore, a potential advantage of combined I-131 MIBG and Y-90-DOTA-TOC therapy was proposed by the researchers, suggesting that the response is optimal; the tumor dose for the combined agents may be achieved when the dose per activity, delivered to the tumor by Y-90-DOTA-TOC, is 2–3 times higher than that of I-131-MIBG.

Patients should always be evaluated by preceding SST scintigraphy and dosimetry, using respective octreotide or lanreotide analogues, preferably the Ga-68-labeled ones for PET. F-18-fluorodeoxyglucose F-18-FDG PET scanning shows a poor sensitivity to detect NET with a low metabolic activity and slow growth rate, while together with the Ga-68-labeled SST analogues, F-18-FDG PET has clinical potential for the metabolic restaging of patients undergoing PRRT. The role of other PET radiopharmaceuticals, C-11-5-hydroxytryptophan (HTP) and F-18-L-Dopa, for patients with NET has to be comparatively assessed, and tumors may show an unbelievable variation.

In general, there is a need for randomized PRRT trials in order to establish which treatment scheme and which radiolabeled SST analogue, or combination of analogues, is optimal for PRRT.

Clinical case

Case 1: Suspicion of MEN I Syndrome

History:

A 57-year-old male, with prolactin hypersecreting adenoma of the hypophysis, neuroendocrine tumor localized at the level of the duodenum and body of pancreas, surgically treated, bilateral suprarenal incidentaloma.

Clinical examination:

Symptoms: abdominal pain, unrelated with meals; diarrhea; fatigue; headache. The patient had important weight loss during the last 2 months; the presence of a post-surgical scar in the abdominal area. After the surgical treatment of the duodenal ulcus and pancreatic resection, he continues to express abdominal pain.
Examinations:
Serum level of PRL: 134 ng/mL (N.V. 1.8–17 ng/mL), increased
Serum level of chromogranin A: 4,551 ng/mL (N.V. 19.4–98.1 ng/mL), very increased
Serum level of gastrine: 14,239 pg/mL (13–115 pg/mL), very increased
Abdominal CT findings: low-density nodular lesion pre- and post-contrast localized at the level of pancreas body (23/19/28 mm); homogenous well-defined nodular lesion with a low uptake of I.V. contrast localized in the right suprarenal gland (23/13/22 mm); the same aspect in the left suprarenal gland (38/35/30 mm)
Cerebral MRI findings: nodular lesion localized at the level of hypophysis gland (10/12/13.5 mm)
Findings:
The scintigraphy with In-111 DTPA octreotide revealed in the early image at 4 h the pathologic uptake in the abdomen, related to the image described at CT in the pancreas (Fig. 10.2). The pathologic uptake was persistent at 24 h, confirmed on SPECT (Fig. 10.3).

Fig. 10.2 In-111 octreotide scan at 4 h post-injection. Pathological uptake in the area of the pancreas

Fig. 10.3 In-111 octreotide scan at 24 h post-injection. Better visualization of the pathologic uptake in the area of the pancreas

Conclusion:
Pancreatic lesion with positive uptake of somatostatin analogue tracer.

Case 2: *Inherited phaeocromocytoma-paraganglioma*

History:
A 42-year-old male, with severe, uncontrolled high blood pressure and right adrenal incidentaloma. Retroperitoneal paraganglioma, lateral from urinary bladder, operated 6 years earlier, and thorax paraganglioma operated one year before the actual presentation.

Clinical examination:
Symptoms: fatigue; headache, sweating and atrial fibrillation. The patient had mild weight loss during the last 2 months (4 kg);
Examinations:
Serum level of chromogranin A: 198 ng/mL (N.V. 19.4–98.1 ng/mL), increased
Serum level of catecholamine: norepinephrine – 1100 pg/mL (N.V. 70-750 pg/mL) and epinephrine <110 pg/mL
Thorax and abdominal CT findings: low-density well-defined nodular lesion pre- and post-contrast localized in the right suprarenal gland (12/10/11 mm);
PGL4 -germline mutation SDHB (succinate dehydrogenase B);

- 20-25% paraganglioma associated with pheocromocytoma,
- 50% thorax-abdominal paraganglioma,
- 20-30% head&neack paraganglioma,
- 20-25% are multifocal
- 14% occurs renal cancer
- and 30% might be malignant

No pathologic findings on cerebral MRI.
Findings:
The scintigraphy with In-111 DTPA octreotide revealed in the early image at 2 h the pathologic uptake in the mediastinum and in pelvic area (Fig. 10.3). The pathologic uptakes were persistent at 4 h, with better visualization, but no other precise details about the localization (Fig. 10.4)
The SPECT/ CT at 24h (Figs. 10.5, Fig. 10.6, Fig. 10.7 and Fig. 10.8) reveal the intense uptake of the tracer at metastatic sites in pelvic bones, thoracic spine, sternum. No uptake in adrenal gland.

Conclusion:
Syndrome phaeocromocytoma-paraganglioma PGL4, SDHB
Comments
If hereditary PGL is known or strongly suspected in a patient presenting with an index tumor, then imaging from neck to pelvis should be performed to exclude synchronous lesions; 68Ga-DOTATATE PET imaging may be appropriate in this regard;

Fig. 10.4 In-111 octreotide scan at 2 h post-injection. Pathological uptake in the mediastinum and pelvic area (a, AP incidence and b, PA incidence)

Fig. 10.5 In-111 octreotide scan at 24 h post-injection. Better visualization of the pathologic uptake in the mediastinum and pelvic area (c, AP incidence and d, PA incidence).

Fig. 10.6 In-111 octreotide scan SPECT/CT at 24 h post-injection. Pathological uptake in the pelvic bones (a-SPECT; b-CT; c-fused image SPECT/CT)

Fig. 10.7 In-111 octreotide scan at 24 h post-injection. Pathologic uptake in the thoracic spine and sternum (a-SPECT; b-CT; c-fused image SPECT/CT)

Fig. 10.8 In-111 octreotide scan at 24 h post-injection. Pathological uptake in the thoracic spine (a- SPECT; b-CT; c-fused image SPECT/CT)

Case 3: *Functionally inactive NET of the ileum*

History:
A 52-year-old male, with intermittent abdominal pain in the last 8 months was admitted for the occurrence of an acute jaundice.
Clinical examination:
Symptoms: fatigue; headache, loss of appetite, weight loss of 6 kg in the last 6 months, nausea. The patient had an acute episode of jaundice.
Examinations:
Serum level of chromogranin A: 78 ng/mL (N.V. 19.4–98.1 ng/mL), normal
Serum level of catecholamine: norepinephrine and epinephrine – normal
Urinary 5-HIAA- 212 mg/24h (N.V. 2-8 mg/24h)
Thorax and abdominal CT findings: multiple hypodense masses in the liver (Fig. 10.9)
Findings:
The scintigraphy with Tc-99m Tektrotyd revealed in the early image at 2 h the pathologic uptake in the multiple tumor masses of the liver (Fig. 10.10). No pathologic uptake visualized in the rest of the body.
The SPECT/ CT at 24h (Fig. 10.11) reveal the intense uptake of the tracer at metastatic sites in liver and the primary tumor in the ileum.
Conclusion:
Ileum NET cu liver metastases expressing the receptor for somatostatin, with positive SSR scan.
Comments
In the case of patients with relapsing abdominal pain, as a result of intestinal pseudo-obstruction by a functionally inactive NET of the lower jejunum and ileum the clinician should note the possibility of NET tumors and the evaluation in this direction should be carried on.

Fig. 10.9. CT image in transversal section showing multiple hypodense masses in liver, suggestive for metastases

Fig. 10.10 Tc-99m Tekrotyd scan at 2 h post-injection. Pathological uptake in the liver area, suggesting multiple metastases expressing SSR (a, AP incidence and b, PA incidence)

Fig. 10.11 Tc-99m Tekrotyd scan at 24 h post-injection, coronal section. The image reveal intense uptake of the tracer in the metastatic lesions of the liver and in the primary tumor in the ileum (fused image

SPECT/CT).

One of the most suggestive example of theranostic, regarding the successful merging of diagnosis and therapy, is the selective, highly specific and systemic role of nuclear tracers in NET. The positive image demonstrates the signature of the tumor in the spectrum of somatostatin receptors, fact that leads further to the use of those molecules targeted selectively for NET and linked with the therapeutic isotopes (Fig.10.12).

Fig. 10.12 The principle of theranostic in NET

Further Reading

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