HOSPITAL CHRONICLES 2012, 7(2): 81–90

REVIEW

The Role of Nuclear Medicine in Imaging and Therapy of Neuroendocrine Tumors

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KEY WORDS: *Neuroendocrine tumors; ^{111}In-pentetreotide; octreoscan; metaiodobenzyluanidine; positron emission tomography*

ABBREVIATIONS:
CEA = carcinoembryonic antigen;
11C-HTP = 11C-hydroxy-tryptophan;
CT = computed tomography;
DMSA = dimercaptosuccinic acid;
FDG = fluoro-deoxy-glucose;
^{18}F-DOPA = fluorodopamine;
GEP = gastro-entero-pancreatic tumors;
MEN = multiple endocrine neoplasia;
MIBG = metaiodobenzyluanidine;
MTC = medullary thyroid cancer;
NETs = neuroendocrine tumors;
PET = positron emission tomography;
PRRT = peptide receptor radionuclide therapy;
SCLC = small cell lung cancer;
SPECT = single-photon emission computed tomography;
VIP = vasoactive intestinal polypeptide

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Manuscript received January 4, 2012;
Revised manuscript received March 3, 2012; Accepted March 10, 2012

ABSTRACT

Neuroendocrine tumors (NETs) constitute a heterogeneous group of tumors characterized by the simultaneous expression of specific marker proteins and cell type-specific hormonal products. Metaiodobenzyluanidine (MIBG), labelled with ^{131}I or ^{123}I, and ^{111}In-pentetreotide (octreoscan) are the radiopharmaceuticals of choice in current clinical practice. Positron emitting radiopharmaceuticals that are used in positron emission tomography (PET) imaging are ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-fluorodopamine (^{18}F-DOPA), ^{11}C-hydroxy-tryptophan (^{11}C-HTP), and Gallium-68 (^{68}Ga-DOTATATE or DOTATOC). For the diagnosis of gastroenteropancreatic neuroendocrine tumors (GEPs), octreoscan is the preferred imaging method because of its high sensitivity. The ^{131}I/^{123}I-MIBG scintigraphy is useful to characterize and locate intra-adrenal (pheochromocytomas) and extra-adrenal paragangliomas. Octreoscan has also high accuracy for extra-adrenal paragangliomas. Also, ^{18}F-FDG-PET or PET/CT seems to be useful in detecting the pheochromocytomas and GEPs that fail to concentrate MIBG and octreocan. The ^{123}I-MIBG scintigraphy combined with urine analysis of catecholamine metabolites is the most sensitive indicator of neuroblastoma. For the diagnosis of small cell lung cancer and pituitary adenomas, octreoscan has a high sensitivity. On the contrary, in medullary thyroid cancer the sensitivity of octreoscan and ^{131}I/^{123}I-MIBG is low but sensitivity of ^{18}F-FDG PET or PET/CT and ^{68}Ga-DOTATATE and DOTATOC PET or PET/CT seems to be higher. With the introduction of ^{131}I-MIBG and octreotide labelled with several radioisotopes, the field of treatment with radionuclides has been extended to a wide range of NETs. Firstly, ^{111}In-DTPA-octreotide was used in some clinical trials but recent advances in somatostatin analogues have paved the way to the development of new radiopharmaceuticals labelled with ^{177}Lu and ^{90}Y radionuclides.

INTRODUCTION

Neuroendocrine tumors (NETs) constitute a heterogeneous group of tumors embracing all neuronal and endocrine elements sharing a common phenotype, characterized by the simultaneous expression of specific marker proteins and cell type-specific hormonal products.[1] Although estimates vary, the annual incidence of clinically significant neuroendocrine tumors is approximately 2.5-5 per 100,000; two thirds are carcinoid

All the authors state that there is no conflict of interest and financial support. All the authors also state that the manuscript is original and has never been published before.

tumors and one third other NETs.[2] The prevalence has been estimated as 35 per 100,000, and may be considerably higher if clinically silent tumors are included.[2] The various kinds of cells that can give rise to NETs are present in endocrine glands and are also diffusely distributed throughout the body, most commonly Kulchitsky cells or similar enterochromaffin-like cells, that are relatively more common in the gastrointestinal (56%) and pulmonary systems (12%).[3]

Neuroendocrine tumors can range from benign lesions to highly aggressive cancers. On the basis of their anatomical and clinical features, NETs can be classified into different types (Table 1).[1,4] Diagnosis of NETs has represented a major challenge in the past decades mostly because of their slow metabolism and for the fact that they often present as small lesions with variable anatomical localization.[5] They also pose significant challenges because of the heterogeneous biology of the tumors. Structural imaging techniques have suboptimal sensitivity in most published series and diagnosis is often delayed until metastatic disease is present. Current guidelines emphasize the importance of functional imaging for evaluating the extent of NETs.[6]

Metaiodobenzyluanidine (MIBG), labeled with ^{131}I or ^{123}I, and DTPA-D-Phe-octreotide, labeled with ^{111}In, are the radiopharmaceuticals of choice in current clinical practice.[7] Also, positron emitting radiopharmaceuticals are used, like ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-fluorodopamine (^{18}F-DOPA), ^{11}C-hydroxy-tryptophan ^{11}C- (HTP), and Gallium-68 (^{68}Ga-DOTATATE or DOTATOC).[8] New radiopharmaceuticals based on somatostatin analogues are under investigation.[7,9] Radiolabelled monoclonal antibodies (anti-CEA and anti-chromogranin-A) can be considered either of historical or experimental value and the use of ^{99m}Tc(V)-DMSA is going to be abandoned.[7] In this review we present the radiopharmaceuticals that are used in diagnosis and therapy of the most frequent types of NETs (Table 2).

TABLE 1. Classification of neuroendocrine tumors

Types of neuroendocrine tumors
• Neuroendocrine tumors of the gastro-entero-pancreatic (GEP) tract: pancreatic endocrine tumors and neuroendocrine tumor of the stomach, duodenum, jejunum, appendix and caecum, colon and rectum
• Tumors of sympatho-adrenal lineage: pheochromocytomas, paragangliomas, neuroblastomas
• Medullary carcinoma of the thyroid gland (MTC)
• Neuroendocrine tumors of the lung: pulmonary carcinoid tumors, small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC of the lung)
• Neuroendocrine tumors of the anterior pituitary
• Several inherited conditions: multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2) von Hippel-Lindau (VHL) disease, neurofibromatosis type 1, tuberous sclerosis, Carney complex
• Merkel cell carcinoma of the skin
• Parathyroid tumors

TABLE 2. Radiopharmaceuticals of choice for neuroendocrine tumor imaging in current clinical practice

Radiopharmaceutical labelled with a radionuclide that emits γ radiation
Metaiodobenzyluanidine (MIBG), labelled with ^{131}I or ^{123}I
^{111}In-pentetreotide (Octreoscan)
^{99m}Tc-Depreotide (Neospect)
^{99m}Tc-EDDA/HYNIC-Tyr^3-Octreotide (Tektrotide)
Radiopharmaceutical labelled with a positron-emitting radionuclide (β $^+$)
^{18}F-fluorodeoxyglucose (^{18}F-FDG)
^{18}F-fluorodopamine (^{18}F-DOPA)
^{11}C-hydroxy-tryptophan (^{11}C-HTP)
^{68}Ga-DOTATATE or DOTATOC).
Treatment with radiolabelled somatostatin analogues
[^{111}In-DTPA^0]octreotide
[^{90}Y-DOTA^0, Tyr^3]octreotide
[^{177}Lu-DOTA^0,Tyr^3] octreotate

A. RADIOPHARMACEUTICALS

A1. IMAGING

1.1 Octreoscan

Somatostatin is a regulatory peptide widely distributed in the human body. In the nervous system somatostatin acts as a neurotransmitter, whereas its hormonal activities include the inhibition of the physiologic and tumorous release of growth hormone, insuline, glucagone, gastrin, serotonin, and calcitonin.[10] Its other actions comprise an antiproliferative effect on tumors and also specific regulation of immune responses.[10] Somatostatin action is mediated through membrane-bound receptors, of which five have been cloned (sst1-sst5).[11] They all belong to the family of G-protein-coupled receptors. Somatostatin is a peptide with two forms, containing 14 and 28 amino acids, respectively.[6] Both bind to all subclasses of somatostatin receptors but are rapidly degraded in the blood by peptidases and have a short half life ($T_{1/2}$=1-2 min).[6] Various synthetic somatostatin analogues have been made to increase resistance to peptidases and thereby allow systemic

delivery by virtue of longer circulation times. These synthetic somatostatin analogues have varying affinity for the different types of somatostatin receptors.[6] However, only sst2, sst5 and, to some extent, sst3 have a high affinity for the commercially available synthetic peptides, octreotide, lanreotide and vapreotide.[10] The most widely used is an 8-amino acid peptide, octreotide, with half life $T_{1/2}$= 2,83 days.[11] This peptide has been radiolabelled as [^{111}In] diethylenetriaminepentaacetic acid (DTPA)-octreotide (Octreoscan, Covidien, Petten, The Netherlands).[12] It has highest affinity for sstr2 and is suitable for imaging on a gamma camera.[6]

Somatostatin receptors have been identified in vitro in a large number of human neoplasias. A high incidence and density of somatostatin receptors is found in neuroendocrine tumors, such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer, and small cell lung carcinoma.[12] Tumors of the nervous system including meningioma, neuroblastoma, and medulloblastoma also express very often a high density of somatostatin receptors. But also tumors not known to be classically originating from endocrine or neural cells, such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, sarcoma, and gastric cancer, can express somatostatin receptors. In the majority of these tumors, the somatostatin receptor subtype-2 is predominantly expressed, although low amounts of other somatostatin receptor subtypes may be concomitantly present.[13] It should be emphasized that selected non-tumoral lesions may express somatostatin receptors, like active granulomas in sarcoidosis and inflamed joints in active rheumatoid arthritis.[10] The expression of somatostatin receptors is therefore not specific for tumoral pathologies. Common indications for [^{111}In-DTPA^0] octreotide scintigraphy include the detection and localization of a variety of neuroendocrine and other tumors and their metastases, the staging of patients with neuroendocrine tumors, the follow-up of patients with known disease, and lastly the selection of patients with inoperable and/or metastatic tumors for peptide receptor radionuclide therapy.

Several attempts have been performed in order to label somatostatin analogues with ^{99m}Tc, which is the most available radionuclide. Thus, ^{99m}Tc-EDDA/HYNIC-Tyr^3-Octreotide (Tektrotide) scintigraphy seems to have significant sensitivity and specificity in GEPs and medullary thyroid cancer (MTC).[14] Also, ^{99m}Tc-Depreotide (Neospect) is another commercially available somatostatin analogue that has been approved specifically for the detection of lung cancer in patients with pulmonary nodules.[15]

1.2 MIBG

Metaiodobenzyluanidine (MIBG) is a derivative of guanethidine and acts as an analogue of norepinephrine.[1] It exploits the type 1 uptake mechanism at the cell membrane, and is stored within intracellular storage vesicles.[1] Cellular uptake of MIBG is driven by passive diffusion, or active uptake, and the compound, carried by norepinephrine transporters facilitated by vesicular monoamine transporters, is deposited in intracellular storage granules.[1] Today, ^{131}I-MIBG and ^{123}I-MIBG are both available for diagnostic purposes. Physical considerations - 159KeV photon energy, $T_{1/2}$=13.2h, fewer particulate emissions which lead to favorable dosimetry - and clinical experience indicate that the ^{123}I-labeled agent is a superior radiopharmaceutical, better suited to gamma cameras and intraoperative detection of tumors.[16] It allows better quality images, better photon detection and greater sensitivity. The higher photon flow allows high-quality single-photon emission computed tomography (SPECT) to be carried out, which may be an advantage.[17] Nevertheless, because of its lower cost and easier availability, ^{131}I-MIBG is still used for routine applications.[16] Also, ^{125}I-MIBG is available for in vitro experiments and biodistribution studies in animals but it is reserved.[16]

Metaiodobenzyluanidine (MIBG) is concentrated in sympatho-adrenergic tissues, especially the chromaffin tissue of the adrenal medulla.[1] It localizes to adrenomedullary tumors, hyperplastic adrenal medulla and the healthy adrenal medulla; in addition, carcinoid tumors and MTC can also accumulate MIBG[18]. The efficiency of ^{123}I-MIBG is excellent for the visualization of intra-adrenal (pheochromocytomas) and extra-adrenal (paragangliomas) chromaffin cell tumors, and can identify multiple tumors in patients with familial syndromes, showing a diagnostic sensitivity and specificity of about 90%.[18]

1.3 Positron-emitting radiopharmaceuticals for PET imaging

Positron emission tomography (PET) utilizes the ability of radiolabelled tracers to be taken-up by certain tumours, and thus selectively assesses the function of different metabolic pathways of the specific tissue.[18] Positron-emitting isotopes frequently used for PET imaging include oxygen-15 (^{15}O), nitrogen-13 (^{13}N), carbon-11 (^{11}C), and fluorine-18 (^{18}F).

Somatostatin analogues labelled with positron-emitting radionuclides are used for imaging with PET cameras or hybrid PET/CT cameras with great potential because of two advantages that they have over γ-emitting analogues. First, many of them have a better affinity for the somatostatin receptor subtype-2, which is most commonly expressed by neuroendocrine tumors. Second, the better spatial resolution of PET imaging and the combined anatomical and functional information that obtained with the hybrid PET/CT technique, result in a higher sensitivity of this type of scanning.[12] The positron-emitting radiopharmaceuticals currently available for neuroendocrine tumor imaging may be divided into two grours: tracers that mark cell metabolism – [^{18}F]FDG (fluorodeoxyglucose), [^{18}F]DOPA (fluorodopamine), [^{11}C]HTP ([^{11}C]5-hydroxytryptophan), and tracers being specific ligands for receptors expressed on these cells- [^{68}Ga]DOTA-peptides like [^{68}Ga]DOTA-TOC and [^{68}Ga]

DOTA-TATE, bombesin, vasoactive intestinal peptide-VIP, cholecystokinin-CCK receptor family, glucagone-like peptide.[5]

^{18}F-fluorodeoxyglucose (^{18}F-FDG) was the first tracer used, reflecting the increased glucose uptake in malignant tumors.[8, 18] During the past few years, numerous studies have demonstrated that the uptake of ^{18}F-FDG relates to tumor grade and proliferation status in a wide variety of tumors.[5] In general, low-grade, slowly proliferating tumors take up less ^{18}F-FDG than poorly differentiated, rapidly growing tumors.[5] ^{18}F-FDG, the most commonly used tracer for PET oncological studies, is certainly not the tracer of choice to study well differentiated neuroendocrine tumors.[5] The metabolic pathway synthesizing 5-hydroxytryptamine (5-HT) from 5-hydroxytryptophan (5-HTP) occurs in carcinoids and other NETs and can thus also be used for PET-imaging; ^{11}C-5-HTP is specifically trapped by serotonin producing tumors and this can be further enhanced by the concomitant administration of carbidopa.[18]

A2. RADIONUCLIDE THERAPY

Coupling a radioisotope to a molecule which would specifically bind to tumor cells could deliver an effective radiation dose to the tumor without damage to non-tumor tissues.[19] Tumor heterogeneity may cause incomplete responses unless the radiation delivered can kill the nearby tumor cells that are target-negative; this depends on the cross-fire from the radioisotope localized in or on the target-positive tumor cells.[18]

Increasing understanding of tumor biology at the molecular level has led to the advent of molecular biological agents for use in cancer therapy, allowing targeted treatment of solid tumors based on information about alterations in cellular pathways and the cell cycle genomics, proteomics and epigenetics.[20] With the introduction of ^{131}I-MIBG and, more recently, octreotide labelled with several radioisotopes, the field of treatment with radionuclides has been extended to a wide range of NETs.[18, 21]

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues has become an established method of treatment of disseminated NETs.[22] Peptides used for PRRT need to be designed for high tumor retention. The β-emitters that are suited for therapeutic use and the most frequently used are ^{90}Y-Yttrium (β_{max}=2.3MeV, $T_{1/2}$=64h) and ^{177}Lu-Lutetium (β_{max}=0.5MeV, $T_{1/2}$=161h), bound to octreotide analogues.[23] As high energy β radiation has a long penetration range in tissue, it is less efficient when treating small tumor lesions (<1-2 g), as much of the energy is deposited outside the lesion. Therefore, high energy particles, such as ^{90}Y, have been considered more appropriate for the treatment of larger tumors, whereas low energy particles, such as ^{177}Lu, may be more suitable for the treatment of small lesions.[23] Apart from β-emitters, the auger-emitter ^{111}In has also been used.

Firstly, ^{111}In-DTPA-octreotide was used in some clinical trials but recent advances in somatostatin analogues have paved the way to the development of new analogues, which can be labelled with both ^{177}Lu and ^{90}Y radionuclides and is characterized by a higher affinity for somatostatin receptor type 2 leading to high tumor uptake.[20, 22] Several studies, most of them phase II clinical trials, have been published examining the activity of biologically targeted agents in NETs, and some have shown encouraging results with favourable rates of partial responses or stable disease.[24-26]

Dose-limiting renal toxicity is probably the most important issue in toxicity of PRRT.[23] Positively charged amino acids but also plasma-expanders have been used successfully to reduce kidney re-absorption of radiolabelled octreotide analogues.[23] Acute hematological toxicity is usually mild, no matter which of the radionuclide is used. Liver toxicity may occur in single patients with liver metastases undergoing PRRT.[23]

B. NEUROENDOCRINE TUMORS

B1. GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (GEP)

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a poorly understood group of lesions that encompass a broad category of neoplasms derived from neuroendocrine cells of the gastrointestinal mucosa and the pancreas.[27] The lesions are grouped based on the acceptance that they have a common cell lineage and produce similar secretory products: chromogranin A, synaptophysin, and neuron-specific enolase. The GEP-NET classification includes carcinoids and pancreatic endocrine tumors: insulinomas, gastrinomas, tumors secreting vasoactive intestinal peptide (VIPomas), glucagonomas, somatostatinomas, and non-functional pancreatic NETs. Although they are more rare than adenocarcinomas, the estimated incidence of pancreatic endocrine tumors is about 5 per 1,000,000 population, whereas carcinoids (bronchopulmonary and gastrointestinal) comprise about 0.46% of all malignancies.[28] Although they are categorized together, their clinical behaviour is strikingly divergent in terms of both symptoms and outcome. Thus, the overall 5-year survival rate for all carcinoids is 67.2%, whereas the overall 5-year survival rate for pancreatic endocrine tumors varies from 97% (benign insulinomas) to about 30% in non-functional ones.[28, 29]

The radiolabeled somatostatin analogue, octreotide, can be imaged by a nuclear medicine gamma camera and used to detect primary and metastatic NETs.[20] This modality allows for total body scanning and has high sensitivity - 61% to 100% - depending on tumor subtype. Positive scintigraphy has been associated with expression of the somatostatin receptor subtype 2 and improved overall survival.[30] The addition of single photon emission computed tomography (SPECT) allows for increased anatomic detail to the functional information gained with nuclear imaging.[20]

The overall results from the literature indicate that octreoscan scintigraphy is particularly useful for small bowel

carcinoids, which may be difficult to localize by conventional methods.[7, 31] Reported values for the detection of known carcinoid tumor localizations vary from 80% to nearly 100%.[10] Also, the detection of unexpected tumor sites, not suspected with conventional imaging, is reported by several investigators.[7] More lesions can be visualized with SPECT imaging than planar imaging, so it is mandatory for an accurate evaluation. Imaging of carcinoids is independent of tumor site or hormonal secretion; moreover, distant metastases may be detected by whole body scanning.[7] Due to its high sensitivity, somatostatin receptor imaging can be particularly useful in localizing the tumor site when surgery is planned.[32]

According to the reported data, the sensitivity of octreoscan in endocrine pancreatic tumors varies from 70% to 90%.[7] In patients with gastrinomas the sensitivity is about 90% and studies have shown that the results of this method altered patient management in 47% (Fig. 1).[10] Octreoscan also shows high accuracy in detecting VIPomas and glucagonomas, with a sensitivity of about 75%-85%.[7] However, the sensitivity of the method for the detection of insulinomas is generally lower (50%-69%) due to a smaller number of somatostatin receptors that bind to pentetreotide.[7, 10]

Thus, the impact of octreoscan on patient management is fourfold:[10] 1. It may detect respectable GEP that would be unrecognized with conventional imaging techniques, 2. It may prevent surgery in patients whose tumors have metastasized to a greater extent than can be detected with conventional imaging, 3. It may direct the choice of therapy in patients with inoperable tumors, and 4. It may be used to select patients for peptide receptor radionuclide therapy.

Neospect (^{99m}Tc-depreotide) is another commercially available somatostatin analogue but because of the relatively high abdominal background and the impossibility to perform delayed imaging due to the short half-life of the tracer, it is less suited for the detection of abdominal neuroendocrine tumors.[9] Tektrotide (^{99m}Tc-EDDA/HYNIC-Tyr^3-Octreotide) has important features in common with octreoscan. Moreover, tektrotide has advantages deriving from the optimal physical characteristics of ^{99m}Tc, with improved scintigraphic image quality, easier availability and much lower cost.[14] On the other hand, there is general agreement that ^{123}I/^{131}I-MIBG has only a complementary role to play in the diagnosis of GEP tumors and may occasionally detect lesions that are not visualized with somatostatin receptor scintigraphy.[7]

Although ^{18}F-FDG has been successfully and widely employed in oncology, its uptake is not high in well differentiated neuroendocrine lesions.[34] The majority of NETs that express somatostatin receptors are well differentiated and therefore the role of ^{18}F-FDG PET in these cases is limited.[35] Increased ^{18}F-FDG uptake can be seen in less-differentiated NETs without somatostatin receptors; in such cases the sensitivity of ^{18}F-FDG PET is clearly higher than that of scintigraphy with octreoscan.[8,34] Since scintigraphy with octreoscan fails to visualize 10–20% of GEP tumors, ^{18}F-FDG PET may prove to be useful in certain cases, although this needs to be formally assessed by a prospective trial.[36] Other positron emitter tracers seem to be more promising.[34] The 5-hydroxytryptophan (5-HTP) labelled with ^{11}C has shown an increased uptake in carcinoids. Imaging with ^{11}C-5-HTP PET has been shown to be superior to CT scanning in diagnosing GEP tumors and monitoring their response to therapy.[8] Another PET radiopharmaceutical, ^{11}C-L-DOPA, seems to be useful in visualizing endocrine pancreatic tumors.[34]

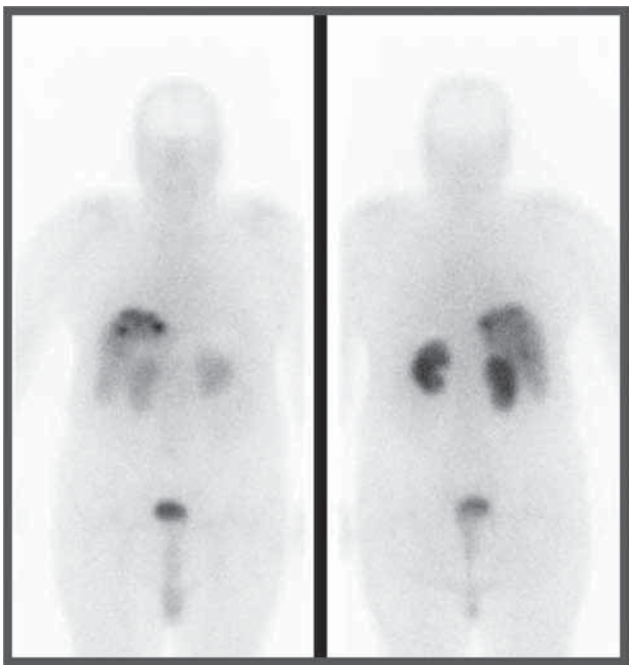

FIGURE 1. Octreoscan images in a 65-year-old man with known pancreatic endocrine tumor (gastrinoma), about 4 years after the initial surgical treatment. Images show recurrence of the disease, with pathological uptake in multiple hepatic lesions

Mapping of the presence of various peptide receptors on the cell membrane by peptide receptor scintigraphy has become an evolving procedure which is non-invasive and without major side-effects, and an easy-to-perform method in the selection of patients for therapy with radionuclides.[37] Treatment with radiolabelled somatostatin analogues (PRRT) is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors.[12] Symptomatic improvement may occur with all ^{111}In-, ^{90}Y-, or ^{177}Lu-labeled somatostatin analogues that have been used for PRRT.[12,25,38]

As at that time no other chelated somatostatin analogues labelled with β-emitting radionuclides were available, early studies in the mid- to late 1990s used [^{111}In DTPA^0] octreotide for PRRT. Initial studies with high dosages of [^{111}In-DTPA^0] octreotide in patients with metastasized neuroendocrine tumors were encouraging with regard to symptom relief, but

partial remissions were exceptional.[39,40] The next generation of somatostatin receptor-mediated radionuclide therapy used a modified somatostatin analogue, [Tyr^3]octreotide, with a higher affinity for the somatostatin receptor subtype-2, and a different chelator, DOTA instead of DTPA, in order to ensure a more stable binding of the intended β-emitting radionuclide Yttrium-90 (^{90}Y). Despite differences in protocols used, complete plus partial responses in most of the different studies with [^{90}Y-DOTA^0, Tyr^3]octreotide are in the same range, in between 10% and 30%, and therefore better than those obtained with [^{111}In-DTPA^0]octreotide.[39,41] The [^{177}Lu-DOTA^0,Tyr^3] octreotate potentially represents an important improvement because of the higher absorbed doses that can be achieved to most tumors with about equal doses to potentially dose-limiting organs and because of the lower tissue penetration range of ^{177}Lu if compared with ^{90}Y, which may be especially important for small tumors. Overall, objective tumor response rate was 46%.[25] It seems that the results that were obtained with [^{90}Y-DOTA^0,Tyr^3]octreotide and [^{177}Lu-DOTA^0,Tyr^3] octreotate are very encouraging in terms of tumor regression. Also, if kidney protective agents are used, the side effects of this therapy are few and mild, and the median duration of the therapy response for these radiopharmaceuticals is 30 and 40 months, respectively.[12]

B2. PHEOCHROMOCYTOMA-PARAGANGLIOMA

The most widely used radiopharmaceutical for the diagnosis of pheochromocytomas is MIBG radiolabelled with ^{123}I and ^{131}I.[7] It is useful to characterize and locate intra-adrenal (pheochromocytomas) and extra-adrenal paragangliomas, it can determine the extent of disease and allows the diagnosis of relapses during postoperative follow-up. Worldwide experience has proved the ability of ^{131}I-MIBG scintigraphy to locate sporadic pheochromocytoma, paragangliomas, chemodectomas and malignant metastatic disease, as well as various familial syndromes associated with pheochromocytomas, including MEN2A and 2B, von Hippel-Lindau syndrome, von Recklinghausen's neurofibromatosis, and simple familial pheochromocytomas.[16] Even non-functional paragangliomas may be visualized, as reported by several authors.[16] The overall diagnostic sensitivity of ^{131}I-MIBG imaging when evaluating the combined data reported in major series is approximately 86%.[7,16,42,43] In malignant pheochromocytomas the sensitivity is higher, 92.4%.[16] Sensitivity improves still further with ^{123}I-MIBG.[16] In fact, ^{123}I-MIBG can visualize a number (~8%) of low MIBG-concentrating pheochromocytomas which cannot be visualized with ^{131}I-MIBG uptake.[16] Radiolabelled MIBG imaging is highly specific as it gives very few (1%-5%) false-positive results and has a high tissue specificity, which permits the nature of the mass to be elucidated.[16]

The sensitivity of octreoscan for pheochromocytoma detection seems to be comparable to that of MIBG but the results depend also on the tumor site, as it is well known that adrenal lesions are difficult to visualize with octreoscan due to its high renal activity.[7] Concerning the paragangliomas, there is clinical evidence that the sensitivity of octreoscan, especially for head and neck paragangliomas, is superior to that of any other nuclear medicine test or radiological procedure, even if MIBG imaging has very good specificity.[7,44] The accuracy of octreoscan is 90%, the sensitivity 94% and the specificity 75%.[7] In fact reports seem to indicate a higher sensitivity of octreoscan in detecting metastatic disease than in localizing benign tumors and in those tumors producing dopamine when MIBG is lacking sensitivity.[7]

Most pheochromocytomas accumulate ^{18}F-FDG and uptake is found in a greater percentage of malignant than benign tumors.[7] These data suggest that ^{18}F-FDG PET can be useful in detecting the pheochromocytomas that fail to concentrate MIBG. A comparison between ^{18}F-DOPA PET and MIBG scintigraphy in the same series of patients showed that the sensitivity of PET was 100% versus 71% for MIBG scintigraphy; both modalities had 100% specificity.[45] Paragangliomas also show marked uptake and retention of ^{18}F-FDG.[7]

Other PET radiopharmaceuticals, such as [^{18}F]FDA, [^{18}F] DOPA, [^{11}C]epinephrine, and [^{11}C]hydroxyephedrine have all been demonstrated to image pheochromocytomas and related neoplasms.[8,41,42]

Examinations with MIBG can also be used to select patients for subsequent radiometabolic therapy on the basis of MIBG uptake by the cancer cells.[7] Before using ^{131}I-MIBG therapy, a diagnostic ^{123}I-MIBG scan is necessary to substantiate the avidity of tumor cells for the radionuclides.[18] The cumulative reported response to ^{131}I-MIBG therapy in patients with phaeochromocytomas and paragangliomas has been extensively reviewed.[46] In the majority of patients clinically symptomatic improvement relating to catecholamine hypersecretion was observed; a biochemical response was almost always associated with a symptomatic response. An overall tumor response (partial tumor response or stabilization of the disease) was obtained in 58% of the patients.[46,47] The reported response to ^{131}I-MIBG therapy is quite heterogeneous, as it depends on several factors including tumor size and extension, ^{131}I-MIBG tumor uptake and retention.[46]

B3. NEUROBLASTOMA

Neuroblastoma is almost exclusively a pediatric neoplasm and the most common extracranial solid tumor in children, accounting for 8%-10% of all childhood cancers.[48] Being a tumor of the neuroblasts of the sympathetic nervous system, the adrenal cells are the commonest site of origin (greater than 50%) followed by other retroperitoneal sites, mediastinum, pelvis and neck.

For neuroblastoma there is a general preference for ^{123}I-MIBG and due to favorable dosimetry and superior image quality the ^{123}I-MIBG scintigraphy combined with urine analysis of catecholamine metabolites is the most sensitive in-

dicator of neuroblastoma.[7,16] Whole-body MIBG scintigraphy, including the limbs and skull as frequent sites for metastases, depicts primary and residual/recurrent neuroblastomas, as well as lesions in bone, soft tissue and bone marrow. It has high sensitivity (93%) and specificity (100%) for the diagnosis of neuroblastomas.[49,50] Addition of SPECT and CT to MIBG scintigraphy can increase the accuracy of both methods.[50] The concordance of ^{123}I/^{131}I-MIBG and octreoscan is about 85%, but there have been patients with only positive MIBG scans.[7]

Most neuroblastomas accumulate ^{18}F-FDG and so ^{18}F-FDG uptake can be shown in neuroblastomas that fail to accumulate MIBG, as the concentration of FDG is not dependent on type 1 catecholamine uptake.[7,51] In patients where ^{123}I/^{131}I-MIBG uptake is not seen, PET using ^{18}F-FDG or other radiopharmaceuticals, might be indicated.[46,51,52]

Therapy with ^{131}I-MIBG is most commonly used in the treatment of neuroblastoma.[53] It was initially reserved for palliation of patients with recurrent disease. However, clinical trials evaluating the role of ^{131}I- MIBG as a first line drug, either as a single agent, or in combination with chemotherapy or myeloablation treatment, have been performed with mixed results and significant potential side effects. The response rates varied between 20% and 60% in newly diagnosed and relapsed or refractory patients.[54] Despite all this information, the precise role of ^{131}I-MIBG in the overall therapeutic strategy of neuroblastoma is far from being defined.

B4. LUNG TUMORS

Somatostatin receptors may be expressed by lung tumors, particularly small cell lung cancer (SCLC) and bronchial carcinoid disease.[55] Octreoscan may have a role to play in the localization and staging of bronchial carcinoid tumors both before and following treatment, and in detecting relapsed disease. Also, octreoscan has high sensitivity in the detection of primary SCLC but the sensitivity is greatly reduced in the detection of metastases.[7] In a recent study, staging with octreoscan successfully located the primary tumor site with a sensitivity of 92%.[56] Although detection of mediastinal lymph node dissemination was also relatively high (83%), octreoscan failed to detect most of the metastatic lesions outside the thorax (25%), while its sensitivity for the detection of malignant lesions in the liver, adrenals, and bones, was 56%, 33% and 17%, respectively.[56]

Various clinical studies have demonstrated the great effectiveness of ^{18}F-FDG PET or PET/CT for disease staging, detection of persistent or recurrent disease, and evaluation of focal opacities.[7] In SCLC, ^{18}F-FDG PET or PET/CT can be considered a valid option for preoperative staging and subsequent treatment monitoring.[57] It is an important tool in the staging work-up of SCLC if performed initially to allow rapid identification of patients with extensive disease, thereby sparing the patient additional radiological or invasive examinations.[58,59] Furthermore, the available clinical data suggest that ^{18}F-FDG PET or PET/CT can provide the basis for determining which treatment modality would be most appropriate during the early stages of SCLC, when surgery is still an option, and that it is a useful tool to assess the response to therapy in treated patients.[60]

The potential role of radiolabelled somatostatin analogues as radiotherapeutic agents in the management of lung cancer is currently being explored.[55] Somatostatin analogue therapy results in significant growth inhibition of both somatostatin receptor-positive and somatostatin receptor-negative lung tumors in vivo. Recent work indicates that these agents may enhance the efficacy of chemotherapeutic agents in the treatment of solid tumors including lung cancer.[55]

B5. MEDULLARY THYROID CANCER

Medullary thyroid cancer (MTC) is rare, accounting for 5%-10% of all thyroid malignancies. It may occur in either sporadic (75%-80%) or hereditary forms (20%-25% of cases).[61] More than 50% of thyroidectomized patients are not cured after surgery, as there is a persistent elevation of basal serum calcitonin levels, which implies residual tumor. There is no single sensitive diagnostic imaging method to reveal all MTC recurrences. Conventional morphologic imaging methods (ultrasound, CT, MRI) frequently fail to reveal the lesions because, after thyroidectomy has been performed, reliable differentiation between scar tissue and recurrent tumor is frequently not possible.[61] The sensitivity of ^{123}I/^{131}I-MIBG was found to be only 31%.[62] In the literature the sensitivity of octreoscan has been reported to be between 37% and 71%.[61] It seems that ^{18}F-FDG PET or PET/CT can play a major role in the follow-up of patients with postoperative elevated plasma calcitonin and the sensitivity for recurrence and residual disease detection per patient are reported to be 47.4%-85% (Fig. 2).[61,63,64] ^{18}F-FDG PET also provides additional information in a significant fraction of cases (up to 54%).[65] Preliminary data suggest that the use of other PET tracers, such as ^{18}F-DOPA and ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE, may provide a better lesion detection rate than does ^{18}F-FDG.[66]

B6. PITUITARY TUMORS

Octreoscan in combination with other imaging modalities is a useful tool in the diagnosis and follow-up of pituitary tumours.[67] This method allows scar tissue to be differentiated from tumor recurrence after the surgical treatment of pituitary adenomas.[70] Somatostatin receptors were demonstrated in vitro in pituitary adenomas producing growth hormone or thyroid stimulating hormone.[7,10] Also, in vivo, octreoscan is positive in most cases, but other pituitary lesions, as pituitary metastases from somatostatine-receptor-positive neoplasms, parasellar meningiomas, lymphoma, or granulomatous diseases of the pituitary may give positive results. Therefore, the diagnostic value of octreoscan in pituitary tumors is limited.[7] It identifies patients with presence of positive receptors for

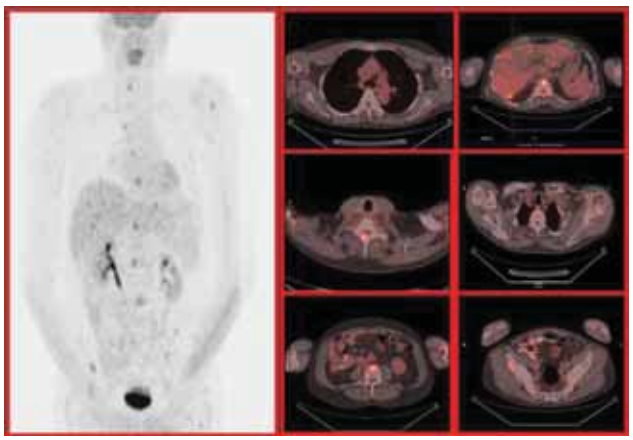

FIGURE 2. [^{18}F]FDG-PET and [^{18}F]FDG-PET/CT images in a 59-year-old man with known medullary thyroid cancer, as part of MEN IIA syndrome and calcitonin levels of 4800pg/ml, about 2 years after the initial treatment. Images show increased uptake of [^{18}F]FDG in multiple hepatic lesions (SUVmax: 6), a precarinal lymph node (SUVmax: 2.9) and in multiple bone lesions (SUVmax: 6.1).

somatostatin, who can then be selected for medical treatment with analogues of somatostatin.[67] Also, pituitary micro- and macro-adenomas may present as hypermetabolic foci on ^{18}F-FDG PET scan.[68]

CONCLUSION

Nuclear Medicine offers functional imaging for evaluating the extent of the heterogeneous group of neuroendocrine tumors (NETs). Metaiodobenzyluanidine (MIBG), labelled with ^{131}I or ^{123}I, and octreoscan are the radiopharmaceuticals of choice in the current clinical practice. In PET imaging, [^{18}F]FDG may not be the ideal radiotracer for imaging these tumors. Preliminary data suggest that the use of other PET tracers, such as ^{18}F-DOPA (^{18}F-dihydroxyphenylalanine) and ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE, may provide a better lesion detection rate. This suggestion needs to be confirmed in larger patient populations. For tumors that demonstrate uptake to a diagnostic scan with ^{123}I- MIBG or octreoscan, therapy with ^{131}I-MIBG or somatostatin analogues radiolabelled with ^{111}In-DTPA, ^{177}Lu or ^{90}Y radionuclides presents a further evolving therapeutic modality. Further data are needed to better acknowledge the role of the integrated use of metabolic and receptor targeted tracers in order to acquire more detailed information regarding the lesion biology and to identify the extent that this could be used to provide the patient with more tailored treatment options.

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