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Imaging of Neuroendocrine Tumors

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Neuroendocrine tumors (NETs) are rare neoplasms, which are characterized by the presence of neuroamine uptake mechanisms and/or peptide receptors at the cell membrane and these features constitute the basis of the clinical use of specific radiolabeled ligands, both for imaging and therapy. Radiolabeled metaiodobenzylguanidine (MIBG) was the first radiopharmaceutical used to specifically depict and localize catecholamine-secreting tumors (pheochromocytomas, paragangliomas, and neuroblastomas) and is still regarded as a first-choice imaging technique for diagnosis and follow-up; in patients with malignant disease, MIBG scintigraphy is an essential step to select patients for ^{131}I-MIBG therapy. Scintigraphy with ^{111}In- or ^{99m}Tc-labeled somatostatin analogs has become the main imaging technique for NETs, particularly those expressing a high density of somatostatin receptors, such as gastroenteropancreatic tumors; this procedure is used routinely for localizing the primary tumor, evaluating disease extension, monitoring the effect of treatment and for selecting patients for radioreceptor therapy. Since the recent development of hybrid machines, it has been possible to obtain images that simultaneously hold both anatomic (computed tomography [CT]) and functional (single-photon emission computed tomography [SPECT] or positron emission tomography [PET]) information, with great impact on diagnostic accuracy. Significant improvements have been made during the past few years with the development of highly specific radiopharmaceuticals for PET studies that reflect the different metabolic pathways of NETs, such as glucose metabolism (^{18}F-fluorodeoxyglucose), the uptake of hormone precursors (^{11}C-5-hydroxytryptophan, ^{11}C- or ^{18}F-dihydroxyphenylalanine, ^{18}F-fluorodopamine), the expression of receptors (^{68}Ga-labeled somatostatin analogs), as well as the synthesis, storage, and release of hormones (^{11}C-hydroxyephedrine and others). Among these radiopharmaceuticals, ^{68}Ga-labeled somatostatin analogs are increasingly used in specialized centers in Europe for PET and PET/CT imaging and show very promising results with high diagnostic sensitivity. New somatostatin analogs with different receptor affinity as well as other peptides are currently under investigation and will further improve our diagnostic and therapeutic capabilities in the future.
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Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from endocrine cells, which are characterized by the presence of secretory granules as well as the ability to produce biogenic amines and polypeptide hormones. These tumors originate from endocrine glands such as the adrenal medulla, the pituitary, and the parathyroids, as well as endocrine islets within the thyroid or the pancreas and dispersed endocrine cells in the respiratory and gastrointestinal tract.[1] The clinical behavior of NETs is extremely variable; they may be functioning or not functioning, ranging from very slow-growing tumors (well-differentiated NETs), which are the majority, to highly aggressive and very malignant tumors (poorly differentiated NETs).[2] Neuroamine uptake mechanisms as well as the presence of peptide receptors and transporters at the cell membrane of several NETs constitutes the basis of the clinical use of specific radiolabeled ligands, both for imaging and therapy. Radioiodinated metaiodobenzylguanidine (MIBG) was the first radiopharmaceutical to be applied for imaging and therapy of some NETs,[3] in particular catecholamine-secreting tumors (pheochromocytomas, paragangliomas, and neuroblastomas), medullary thyroid carcinomas, and carcinoid tumors.[4-9] The field of application of MIBG imaging is still expanding, with great interest for in vivo studies of the adrenergic autonomic innervation of the heart.

Because the majority of NETs express somatostatin (SS) receptors, they can be successfully targeted with radiolabeled

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Table 1 Drugs Known or Expected to Interfere With MIBG Uptake

Mechanism of Interference	Drugs	Suggested Period of Withdrawal (Days)
Inhibition of uptake-1	Cocaine, opioids	7-14
	Tricyclic antidepressants (amitriptyline and derivatives, imipramine and derivatives, amoxapine, ioxapine, doxepine, others)	7-21
	Antipsychotics (phenothiazines,* thiozanthines, butyrophenones)	21-28
	Labetalol, metoprolol	21
Inhibition of granular uptake	Reserpine, tetrabenazine, etc	14
Competition for granular uptake	Norepinephrine, serotonin, guanethidine, etc	14
Depletion of storage granules	Reserpine, guanethidine, labetalol, etc	14-21
	Sympathomimetics† (such as phenylpropanol-amine, amphetamine, dopamine, isoproterenol, salbutamol, etc)	
Increased uptake and retention	Calcium channel blockers	14
	Angiotensin-converting enzyme inhibitors	14

Adapted from Troncone and Rufini.[9]
*Occasionally components of antiemetic and antipruritic agents.
†Components of bronchodilators, decongestants and anoretics.

SS analogs in vivo. After more than a decade of experience, somatostatin receptor scintigraphy (SRS) with ^{111}In-DTPA-octreotide has become the main imaging technique for NETs and is used routinely.[10] Other analogs with different receptor affinity as well as other peptides are under investigation.[11] More recently, great progress has been made in the functional imaging of NETs with the development of highly specific radiopharmaceuticals for PET studies that reflect different metabolic pathways, such as glucose metabolism, the uptake of hormone precursors, the expression of receptors or transporters, as well as the synthesis, storage, and release of hormones.[12] Among these radiopharmaceuticals, gallium-68-labeled somatostatin analogs are increasingly used in specialized centers in Europe.[13,14]

This review will focus on the functional imaging of NETs by means of radioiodinated MIBG and radiolabeled peptides, mainly stressing the use of ^{111}In-DTPA-octreotide. The clinical experience of these radiopharmaceuticals in endocrine tumors, ie, pheochromocytomas and paragangliomas, NETs of the gastrointestinal tract (carcinoids and pancreatic NETs), ectopic adrenocorticotropin hormone (ACTH)-secreting tumors causing Cushing's syndrome, and medullary thyroid carcinoma will be reviewed; also neuroblastoma, a highly malignant pediatric cancer, will be mentioned. Special emphasis will be given to the currently evolving role of new tracers for the PET imaging of NETs.

Radioiodinated MIBG

MIBG structurally resembles the adrenergic neurotransmitter norepinephrine (NE) and, to some extent, shares its biological behavior in that it is taken up by an active, sodium- and energy-dependent amine uptake mechanism (uptake-1) in the cell membrane of sympathomedullary tissues and is stored into the intracellular catecholamine storing granules by another specific, active uptake mechanism.[15] It is the presence of this specific uptake mechanism and the prolonged storage within the neurosecretory granules, which provide the molecular basis for the high specific imaging and therapy with radioiodinated MIBG.[16] ^{131}I-MIBG and ^{123}I-MIBG are both available for diagnostic purposes. Physical considerations (159 keV photon energy, 13.2 hour half-life) and clinical experience indicate that ^{123}I-MIBG is the agent of choice: it allows high-quality single-photon emission computed tomography (SPECT) and has a more favorable dosimetry; the effective dose in adult subjects is 0.013 mSv/MBq for ^{123}I-MIBG and 0.14 mSv/MBq for ^{131}I-MIBG.[17] Possible drawbacks of ^{123}I-MIBG are its higher cost and its limited availability in the United States (^{123}I-MIBG has not yet been approved by the Food and Drug Administration, whereas it is commercially available in Europe),[18] as well as the impossibility of prolonged studies (ie, dosimetry before ^{131}I-MIBG therapy). For these reasons, ^{131}I-MIBG is still used for routine application.

A radiolabeled agent with a negligible cold MIBG content has been synthesized, the so-called noncarrier-added MIBG (nca-MIBG) and proposed both for diagnostic and therapeutic application.[19] Although experimental studies in animals have shown a greater target-to-nontarget ratio,[20] no significant improvement in tumor uptake has been observed in patients with pheochromocytoma studied with nca-^{123}I-MIBG.[21] Nevertheless, nca-MIBG might be the preferred formulation for therapeutic application, due to the reduced molar amount of drug injected and consequently its reduced pharmacological side effects.

Scintigraphic Procedure

To avoid thyroid uptake of "free" radioiodine, it is necessary to block thyroid function with saturated potassium iodide (KI; 1-2 mg/kg per day of potassium iodide beginning 1 day before tracer injection and continuing for 3-5 days); alterna-

tively, potassium perchlorate may be given. Table 1 reports drugs that can alter MIBG uptake through various mechanisms of interaction; they must be withdrawn before imaging to avoid false-negative results. If necessary, phenoxybenzamine (alpha-receptor blockade) and propranolol (beta-receptor blockade) may be administered to control hypertension.[9] Sedation may be necessary for pediatric patients because of the long examination time. The recommended activity to obtain good quality images is 37 to 74 MBq (1-2 mCi) of ^{131}I-MIBG (specific activity ≥74 MBq/mg) or 370 MBq (10 mCi) of ^{123}I-MIBG (specific activity >300 MBq/mg) in adult patients; to avoid potential side effects, ^{123}I/^{131}I-MIBG is administered by slow intravenous injection over the course of 1 to 2 minutes. When ^{131}I-MIBG is used, imaging is performed using a gamma camera equipped with a high-energy, parallel-hole collimator at 24, 48 and, occasionally, 72 to 120 hours (delayed scan) postinjection; a whole-body scan (4 cm/min) and additional spot images of selected areas (>150,000 counts) are obtained. When ^{123}I-MIBG is administered, imaging is performed using a low-energy, high-resolution collimator at 4 (optional), 24, and 48 hours (if indicated) postinjection; a whole-body scan (5 cm/min) or planar images of the entire body (>250,000 counts) are obtained.[17]

Delayed images are useful if nonspecific tracer accumulation is suspected in the kidneys and/or in the bowel. SPECT can significantly improve the diagnostic accuracy of the MIBG study, allowing better delineation and localization of tumor deposits to distinguish small tumors from other physiological or pathological uptake.[22] SPECT studies are acquired at 24 hours after ^{123}I-MIBG administration, using a single or multihead rotating gamma camera, with acquisition parameters depending on the equipment available. Image fusion of MIBG SPECT with CT or magnetic resonance imaging (MRI) or coregistration with CT images may provide a significant impact on diagnostic accuracy.[23] Quantitative measurements of ^{123}I-MIBG to calculate the adrenal medullary uptake have been performed to study adrenomedullary pathophysiology, and concentration measurements by planar and/or SPECT studies have been taken for dosimetric purposes in candidates for ^{131}I-MIBG therapy. Usually, the basic method of geometric mean between conjugate views is used for this purpose.[24]

Normal Scintigraphic Pattern and Interpretation Criteria

Knowledge of the normal biodistribution of MIBG is essential to avoid misinterpretation, and this is particularly important in children. In normal subjects, both ^{131}I-MIBG and ^{123}I-MIBG scans show uptake in the heart, lungs, salivary glands, liver, spleen, colon (in approximately 20% of cases), and bladder. The normal adrenal medulla is seldom seen with ^{131}I-MIBG, whereas it is frequently depicted when ^{123}I-MIBG is used. No bone activity is ever evident. In infants myocardial uptake may be very high.[25] Bilateral symmetrical activity is sometimes evident in the neck and shoulders of children, and it seems to be related to uptake in brown adipose tissue, which is mediated by the sympathetic nervous system.[26,27] Any uptake in nonphysiological areas is suspicious for a NET or its metastatic lesion. False-negative results may be caused by incorrect patient preparation, technical factors (limitation in spatial resolution), or anatomic factors (lesion size and physiological uptake masking tumor lesions). In addition, they can depend on intrinsic tumor characteristics, such as tumor heterogeneity, low or absent specific uptake-1, or rapid tracer washout from the storage pool.[22] Radiolabeled MIBG imaging is characterized by high specificity with very few (1-5%) false-positive findings, ie, as a result of retention of radioactivity in the urinary tract, or the presence of adrenal hyperplasia following contralateral adrenalectomy[28] or very rarely to non-NET or benign lesions.[29]

Clinical Indications

The main indication for MIBG scintigraphy in oncology is the imaging of NETs and in particular catecholamine-secreting tumors, which are visualized with high sensitivity. Because of its characteristics as a "metabolic" tracer, highly specific and with functional marks, MIBG is especially suitable for imaging tumors with functional activity such as pheochromocytomas, functioning paragangliomas, neuroblastomas, medullary thyroid carcinomas and carcinoids. Moreover, because of its tissue specificity, MIBG allows the tissue characterization of the above-mentioned NETs. In patients with malignant disease MIBG scintigraphy is an essential step to select patients for therapy with ^{131}I-MIBG at high specific activity.

Radiolabeled Peptides

Somatostatin Analogs

The many effects of SS and its long-acting analogs are mediated by interaction with specific cell membrane receptors on target cells. To date, 5 specific SS receptor subtypes (sstr1-sstr5) with different tissue distribution have been cloned.[30,31] All subtype receptors bind the native peptide but show major differences in their affinity for SS analogs. SS receptors are overexpressed at the cell membrane of a large variety of NETs, as well as other tumors with various degrees of density[31]; they are expressed also in peritumoral vessels and in inflammatory and immune cells (eg, activated lymphocytes), and this can account for visualization of those tumors whose cells do not express the receptors (ie, non small cell lung cancer). Moreover, the internalization of the peptide-receptor complex favors retention of the radioligand in receptor-positive tumors. In vitro, demonstration of SS receptor expression is provided by in situ hybridization that identifies the mRNA, or by receptor autoradiography and immunohistochemistry, which identify the receptor protein.[32] Although various SS receptor subtypes are expressed in tumors, sstr2 is the predominant one in NETs and clinically used SS analogs bind predominantly to sstr2. So, it is the presence of sstr2 as well as its density, which provides the molecular basis for a number of clinical applications of SS analogs, including symptomatic treatment of hormone-secreting NETs with "cold" octreotide as well as the diagnostic and therapeutic use of radiolabeled analogs.[32]

Table 2 Affinity Profiles (IC_{50}) for the 5 Human SS Receptor Subtypes (SSTR) of Different SS Analogs

Peptide	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Native somatostatin SS-28	5.2	2.7	7.7	5.6	4.0
In-DTPA-octreotide	>10000	22	182	>1000	237
In-DOTA-[Tyr^3]octreotide (DOTA-TOC)	>10000	4.6	120	230	130
Y-DOTA-TOC	>10000	11	389	>10000	114
Ga-DOTA-TOC	>10000	2.5	613	>1000	73
DOTA-lanreotide (DOTA-LAN)	>10000	26	771	>10000	73
DOTA-[Tyr^3]octreotate (DOTA-TATE)	>10000	1.5	>1000	453	547
In-DOTA[1-Nal^3]octreotide (DOTA-NOC)	>10000	2.9	8	227	11.2
Y-DOTA[1-Nal^3]octreotide (DOTA-NOC)	>1000	3.3	26	>1000	10.4
In-DOTA-NOC-ATE	>10000	2	13	160	4.3
In-DOTA-BOC-ATE	>1000	1.4	5.5	135	3.9

IC_{50} values are expressed in nanomoles (lower the value, greatest the affinity).
Adapted from Reubi et al,[30] Ginj et al,[46] and Wild et al.[48]

The cyclic octapeptide octreotide was the first SS analog to be used in clinical practice. This compound has been conjugated with diethylene-triamine-pentaacetic acid (DTPA) and labeled with ^{111}In, showing an improved biodistribution when compared with the initially used ^{123}I-Tyr^3-octreotide, with a shift from a gastrointestinal excretion—that interferes with tumor uptake in the abdominal region—to a prevalent renal excretion. In 1994, ^{111}In-DTPA-octreotide (Octreoscan; Mallinckrodt, St. Louis, MO) was approved by the Food and Drug Administration as an imaging agent for somatostatin receptor-positive NET. In addition to γ-rays, ^{111}In also emits Auger and conversion electrons that may be used for therapy.[33,34] The effective dose for ^{111}In-DTPA-octreotide in adult subjects is 0.054 mSv/MBq.[35] Reubi and Waser[31] have shown that slight structural changes of SS analogs, as well as the substitution of a chelator with another, or metal replacement can markedly affect the binding affinity. Recently, octreotide has been conjugated with the macrocyclic chelator DOTA (1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid), which enables stable labeling with various metal ions (indium, gallium, yttrium, lutetium, copper, and others), resulting in tracers that are suitable for a variety of clinical applications.[36-38]

Clinical studies with radiolabeled DOTA-Tyr^3-octreotide (DOTA-TOC) have shown that these radioconjugates are effective both for imaging (^{111}In-DOTA-TOC, ^{68}Ga-DOTA-TOC) and therapy (^{90}Y-DOTA-TOC).[13,39-44] In addition, replacement of the C-terminal threoninol of the octapeptide with the natural amino acid threonine (ie, changing octreotide to octreotate) increases sstr2 affinity and tumor uptake, with considerable improvement of scintigraphic results.[45,46] All the aforementioned radiopeptides bind with high affinity, mostly to sstr2. Novel radiolabeled SS analogs with a broader sstr profile are already used for receptor PET imaging of NET[14,47] and are becoming more available. Wild and coworkers have developed [^{111}In, ^{90}Y-DOTA]-1-Nal^3-octreotide (^{111}In, ^{90}Y-DOTA-NOC), which shows high binding affinity to sstr2, sstr3 and sstr5 and preliminary clinical trials indicate that DOTA-NOC is superior to the other well-studied SS analogs.[48,49] More recently, Ginj and coworkers evaluated two new DOTA-based peptides, [^{111}In-DOTA-Nal^3Thr^8]-octreotide (DOTA-NOC-ATE) and [^{111}In-DOTA-$BzThi^3Thr^8$]-octreotide (DOTA-BOC-ATE); the reported preclinical data indicate that both radioligands are very promising for clinical application, showing high affinity to sstr2, sstr3 and sstr5 and intermediate affinity to sstr4 (Table 2).[46] DOTA-lanreotide, labeled with ^{111}In for imaging and with ^{90}Y for therapy, was initially claimed as having high binding affinity for all SS receptors except subtype 1[50]; however, these data have not been subsequently confirmed and DOTA-lanreotide shows higher affinity than Octreoscan only for sstr5.[30]

Scintigraphic Procedure

The recommended activity of ^{111}In-DTPA-octreotide to obtain good-quality planar and SPECT images is about 220 MBq (6 mCi) using at least 10 μg of the peptide. Planar and SPECT images are acquired 24 and 48 hours after tracer injection using a gamma camera equipped with medium energy parallel hole collimators.[35] For better interpretation of abdominal images, early imaging at 4 hours (which shows negligible bowel activity) can be useful. When whole body acquisition is performed, scan speed should not exceed 3 to 5 cm/min. An approximate evaluation of receptor density in the tumor may be achieved by calculating the tumor-to-liver ratio in planar images.[45] This measurement is important mainly to assess eligibility for peptide receptor radiotherapy.[51] A semiquantitative measurement of ^{111}In-octreotide uptake based on the analysis of the tumor/background ratio calculated on SPECT images acquired at 4 and 24 hours postinjection, may increase the specificity of tumor detection; also it has been proposed as a prognostic parameter in NETs of the gastrointestinal tract.[52,53]

Uptake of radiolabeled octreotide is reduced in the presence of high concentrations of unlabeled octreotide that block the receptor binding. So, in patients on chronic therapy it is advisable to withdraw the octreotide immediate-release formulation 24 hours before scintigraphy.[54] In patients treated with long-acting formulations, SRS should be performed just before the next long-acting formulation administration.[55] However, in patients with severe symptoms, the maintenance of octreotide therapy seems not to influence

Table 3 Potential Receptors Other Than SS Receptors for Clinical Use

Peptide	Receptor Subtypes	Tumor Expression	Radiolabeled Peptides	References
Bombesin/GRP	GRP-R	Prostate cancer, breast cancer, GISTs, SCLC	^{99m}Tc-bombesin ^{111}In-bombesin, ^{68}Ga-bombesin	59-65
CCK/gastrin	CCK_2	MTC, insulinoma, SCLC, GISTs	^{111}In-DTPA-minigastrin ^{99}Y-minigastrin	64,66-68
GLP-1	GLP-1-R	Insulinoma, gastrinoma	^{123}I-GLP-1	69,70
Neuropeptide-Y	NPY-R	Breast cancer, ovarian and adrenal tumors	^{99m}Tc-neuropeptide Y	71,72
Neurotensin	NT-R1	Exocrine pancreatic cancer, Ewing sarcoma, meningioma	^{99m}Tc-neurotensin	73
Substance P	NK1	Glial tumors	^{90}Y-DOTAGA-Substance P	74,75
VIP	$VPAC_1$	Gastro-intestinal and other epithelial cancers	^{123}I-VIP ^{99m}Tc-TP3654	57,76

GRP-R, gastrin releasing peptide–receptor; CCK, cholecystokinin; GLP, glucagon-like peptide; VIP, vasoactive intestinal peptide; VPAC, VIP–pituitary adenylate cyclase-activating polypeptide; NK, neurokinin; GISTs, gastrointestinal stromal tumors.

SRS results.[54] To avoid artifacts in interpretation of abdominal images, the use of a mild oral laxative might be useful.

Normal Scintigraphic Pattern and Interpretation Criteria

Normal scintigraphic pattern includes visualization of organs, which express SS receptors, including the thyroid, spleen, liver, kidneys and, in some patients, the pituitary. Other organs are depicted at different times as a result of tracer excretion, including the renal collecting system and urinary bladder, gallbladder, and bowel.[35] Any uptake in nonphysiological areas reflects the presence of lesions with increased density of SS receptors, which can be related to malignant but sometimes also to benign lesions. Sensitivity of SRS in different tumor types is related to various factors such as type and density of SS receptors expressed by the tumor, target-to-background ratio, and tumor site and tumor histology. It is important to stress that uptake is sometimes also visible in tumors other than NET as well as in granulomas and autoimmune diseases, but overall specificity is high. Therefore, it is most important that interpretation of SRS is performed in close relation to the clinical symptoms and the history of the patient.[56]

Clinical Indications

SRS is mainly used for the detection and localization of NETs, particularly those expressing a high density of SS receptors, such as gastroenteropancreatic (GEP) tumors. In this tumor type, there is not only the largest experience with SRS but also a substantial consistency of the results obtained. The information of SRS is exquisitely functional, reflecting the physiological and pathological distribution of SS receptors and cannot be obtained by morphologic imaging techniques. Moreover, SRS may have prognostic significance because SS receptors are found mainly in well differentiated rather than poorly differentiated tumors. In patients with NET, SRS is mainly used for localizing the primary tumor, evaluating disease extension, monitoring the effects of treatment, as well as a prognostic parameter in predicting the response to therapy, and for selecting patients for therapy with unlabeled or labeled SS analogs.

Other Radiolabeled Peptides

Although the initial results obtained with ^{123}I-VIP (vasoactive intestinal peptide) suggested a potential clinical role of this radiolabeled peptide, difficulties emerged inherent to the targeting of this receptor in vivo mainly because of its ubiquitous distribution in normal tissues, thus limiting its widespread clinical use.[32,50,57] Recently, other peptide receptors have been demonstrated to be overexpressed with higher incidence and/or density than SS receptors in various NETs and non-NETs[58]; the corresponding radiolabeled peptides are under investigation and some of them, such as ^{111}In-DTPA-D-Glu(I)-minigastrin for medullary thyroid carcinomas, ^{99m}Tc-bombesin for breast and prostate carcinomas, and radiolabeled glucagon-like peptide for insulinomas, appear to have promising potential for clinical applications (Table 3).[31,57,59-76] Furthermore, the simultaneous expression of multiple peptide receptors in NETs provides the molecular basis for in vivo multireceptor targeting (eg, glucagon-like peptide and cholecystokinin radioligands for insulinomas; or sstr2, glucagon-like peptide and gastrin-releasing peptide radioligands for gastrinomas), thus improving the efficacy of radiolabeled peptides both for diagnosis and therapy.[32,58]

PET Radiopharmaceuticals

A variety of biological substances can be labeled with positron emitters such as ^{11}C, ^{15}O, ^{13}N, and ^{18}F without changing the molecular structure or characteristics. At present, the tracers available for PET imaging allow the visualization of more the 90% of NETs. The goal of PET is to detect abnormalities before morphological changes occur and assess the function of different metabolic pathways of the specific tissue, using radiolabeled tracers that are selectively taken up by the tumors.

^{18}F-Fluorodeoxyglucose (FDG) is the glucose analog most used in oncology with very high sensitivity in many types of

tumors, especially the rapid-growing and aggressive ones.[77] FDG uptake in neoplastic cells is related to the regional blood flow and reflects the highest glucose metabolism; moreover, it is linked to the cellular proliferative activity.[78] Tumors with high FDG uptake seem to be more aggressive and are associated with a less-favorable prognosis.[77] The activity administered to the adult is 340 to 740 MBq (9.2-20 mCi) and imaging is acquired 60 minutes after injection; the effective dose in adults is 0.019 mSv/MBq.[78] There is no evidence of drugs interfering with FDG uptake; however, patients should fast for 6 to 12 hours before testing. Pitfalls in the interpretation of FDG images may be caused by the "physiological" activity in the brain, vocal cords, esophagus, heart, stomach, bowel, bladder, and brown fat. The usefulness of FDG-PET in the diagnosis of NET also depends to some extent on the grade of differentiation and their biologic aggressiveness. In fact, it is well known that NET are mostly well-differentiated and slow-growing tumors, and not all tumors take up FDG.[77,79-82] Therefore, a more systematic analysis is needed to define the role of FDG-PET, as some slowly growing tumors also show high FDG uptake (Baum RP, personal observation).

Various PET agents share with MIBG the catecholamine transport and storage mechanisms, eg, ^{11}C-epinephrine (^{11}C-E), ^{11}C-hydroxyephedrine (^{11}C-HED), ^{18}F-fluorodopamine (^{18}F-FDA), and L-dihydroxyphenylalanine (L-DOPA) labeled with ^{11}C or ^{18}F. ^{11}C-E and ^{11}C-HED are catecholamine analogs developed for studying the sympathetic nervous system as well as for characterizing and localizing pheochromocytomas and neuroblastomas, thanks to their high and selective uptake in organs rich in sympathetic innervation.[83-86] However, their widespread clinical use is limited by the short physical half-life of ^{11}C and high costs.

^{18}F-FDA is a catecholamine precursor that has been developed at the National Institutes of Health (NIH). ^{18}F-FDA binds to the NE transporter at the cell membrane and is internalized into cytoplasmatic vesicles,[87] allowing the visualization of the sympathetic cells. The activity administered is 370 to 740 MBq (10-20 mCi) and imaging can start almost immediately after injection. ^{18}F-FDA-PET is characterized by almost-absent false-positive results; false-negative results can be attributed to tumor dedifferentiation.[88] ^{18}F-FDA has been used in patients with adrenal and extra-adrenal pheochromocytoma and other chromaffin tumors, providing excellent results.[89,90]

L-DOPA is an amino acid that is converted by aromatic amino acid decarboxylase to dopamine. L-DOPA labeled ^{11}C or ^{18}F is employed as a PET tracer for dopamine synthesis. There are few published data concerning clinical applications of DOPA labeled ^{11}C, owing to less tracer availability and its high costs. The administered activity of ^{18}F-DOPA in adults is 200 to 300 MBq (5.4-8 mCi) and imaging is acquired 45 to 90 minutes postinjection. Potential limitation of ^{18}F-DOPA is the physiological uptake in the abdomen, which might mask tumors in this site; premedication with carbidopa can be useful. The radiation exposure is low: 2.7mSv/100MBq.[91] Literature shows that a large variety of NETs such as pheochromocytomas, medullary thyroid carcinomas, glomus tumors and GEP NET can be depicted using L-DOPA.[81,91-95]

^{11}C-5-hydroxytryptophan-labeled ^{11}C (^{11}C-5-HTP) is specifically and irreversibly trapped by serotonin-producing tumors.[96,97] The activity administered to the adult is 250 to 450 MBq (6.7-12 mCi) and imaging is acquired 10 minutes after injection. To increase the tumor-to-background ratio, it is advisable to administer carbidopa (100-200 mg 60 minutes before injection), thus facilitating image interpretation.[55,96,98] ^{11}C-5-HTP accumulation is not affected by fatty changes induced from treatment (such as interferon), whereas this condition constitutes a problem on CT. Nonfunctioning or poorly differentiated tumors or necrotic ones can be difficult to detect with ^{11}C-5-HTP.[96,98] Unfortunately, ^{11}C-5-HTP can only be produced in centers with a cyclotron on site and at high costs, and extensive use is therefore limited.

Radiolabeled SS Analogs for PET

New peptides DOTA-TOC and DOTA-NOC have been developed recently[13,47,48] and are becoming the gold standard of ^{68}Ga-labeled peptides. Preclinical data suggest that these radiotracers are superior to existing radiolabeled SS analogs, having a higher affinity for sstr2 but, most important, also for sstr5 (mainly DOTA-NOC). ^{68}Ga (physical half-life 68.3 minutes) is eluted from an in-house ^{68}Ge-generator (physical half-life 270.8 days by electron capture) that allows a continuous tracer production. DOTA-TOC or DOTA-NOC can be easily and quickly labeled with ^{68}Ga, and synthesis results in a product with high radiochemical purity.[99,100] The ^{68}Ga-labeled peptides show a rapid renal clearance and are rapidly accumulated in the tumors (80% within 30 minutes); concentration in tissues without expression of SS receptors is low, providing higher contrast imaging.[100,101] The activity administered in adults is 100 to 150 MBq (2.7-4 mCi) and imaging is acquired 60 to 90 minutes after injection. Semiquantitative measurements (ie, standardized uptake value, SUV) by using ^{68}Ga-labeled SS analogs are useful before and after radiopeptide therapy.

^{64}Cu is an attractive radionuclide for PET imaging (physical half-life 12.7 hours), which can be obtained by either a reactor or a medical cyclotron. Due to the high rate of lesion detection, sensitivity and favorable dosimetry and pharmacokinetics, ^{64}Cu-TETA-octreotide is a promising tracer for PET imaging in patients with NETs.[38,102]

A novel carbohydrated analog of octreotide labeled ^{18}F, ^{18}F-fluoropropionyl-Lys^{0}-Tyr^{3}-octreotate (^{18}F-FP-Gluc-TOCA), is under investigation.[103] Preliminary data indicate that the biodistribution of ^{18}F-FP-Gluc-TOCA resembles that of other somatostatin tracers such as ^{68}Ga-DOTA-TOC, suggesting its use in somatostatin-receptor-positive tumors.

Pheochromocytoma and Paraganglioma

Clinical Presentation and Diagnosis

Pheochromocytomas are rare catecholamine-secreting NETs arising from chromaffin cells of the adrenal medulla, whereas paragangliomas are chromaffin cell tumors arising in the sympathetic and parasympathetic paraganglia; the latter are

located from the base of the skull to the urinary bladder and may be functioning or not functioning. The prevalence of pheochromocytoma is estimated at 0.5% of patients with hypertension and evocative clinical symptoms and is as high as 4 to 6.5% in patients with adrenal incidentaloma.[104-106] Most catecholamine secreting tumors are larger than 2 cm in diameter and reside in one of the adrenal glands. However, a substantial portion (10-20%) are multiple, extra-adrenal or malignant. The presence of a pheochromocytoma or functioning paraganglioma is usually suggested by the clinical symptoms or family history of a patient with familial disease. The diagnosis is confirmed by measurements of urinary and plasma catecholamines and their metabolites. Imaging studies to locate the tumor follow the biochemical diagnosis. In sporadic tumors both CT and MRI are highly sensitive (98-100% sensitivity); however, sensitivity of CT decreases in patients with multiple endocrine neoplasia type 2 (MEN 2) syndrome, and in patients with extra-adrenal, recurrent or metastatic lesions.[106,107] Moreover, both CT and MRI have low specificity (approximately 70%), because of the high prevalence of adrenal "incidentalomas."

Radionuclide Imaging

Radiolabeled MIBG

At MIBG scintigraphy, benign tumors are depicted as foci of increased MIBG uptake in the adrenal or extra-adrenal sites, whereas multiple areas of uptake outside the adrenal and sympathetic ganglia characterize malignant tumors. Worldwide experience has proved the ability of ^{131}I-MIBG scintigraphy to locate pheochromocytomas and paragangliomas of all types, including adrenal and extra-adrenal tumors, and metastatic disease as well as pheochromocytomas associated with various familial syndromes (eg, MEN 2A and 2B, von Hippel–Lindau syndrome, von Recklinghausen's neurofibromatosis), and simple familial pheochromocytomas[4,108-111]; also, pheochromocytomas with normal or mildly increased urinary catecholamine metabolites are successfully depicted.[112] The overall diagnostic sensitivity of ^{131}I-MIBG imaging when evaluating the combined data reported in major series is approximately 86%.[9,113-117] Sensitivity further improves with ^{123}I-MIBG and the use of SPECT and this radiopharmaceutical should be the agent of choice. In fact, ^{123}I-MIBG can visualize a number (approximately 8%) of low MIBG-concentrating pheochromocytomas, which cannot be visualized with ^{131}I-MIBG.[118] The use of an intraoperative gamma-probe after injection of ^{123}I-MIBG may be useful for detecting and removing small recurrent tumors in the adrenal region.[119,120] False-negative MIBG scans may be expected if medication that interferes with MIBG uptake is not withdrawn before imaging, and in presence of small tumors (< 1 cm) or medullary hyperplasia (MEN 2A/2B-related) or large and highly necrotic or dedifferentiated masses.[121] On the whole, MIBG scintigraphy is a safe, efficacious, noninvasive technique in patients with biochemical proven pheochromocytoma or functioning paraganglioma; it has the advantage of tissue specificity and the capability of screening the whole body. Therefore, also in patients in whom CT or MRI depicted an adrenal tumor, MIBG scintigraphy can easily confirm that the tumor is indeed a pheochromocytoma, and detect any extramedullary tumor and multifocal or malignant disease (Fig. 1). Additionally, it is especially indicated after surgery, when anatomic alterations or the presence of metallic clips allow only suboptimal results from anatomic imaging modalities and as a prelude to ^{131}I-MIBG therapy.[122]

Radiolabeled SS Analogs

In benign pheochromocytoma/paraganglioma the initially reported sensitivity of ^{111}In-DTPA-octreotide scintigraphy was 88%, similar to that of MIBG scintigraphy. In a large retrospective study of patients with primary benign pheochromocytomas, Van der Harst and coworkers report an overall detection rate of 25% for SRS versus 90% for ^{123}I-MIBG.[121] Therefore, in case of benign adrenal tumors ^{111}In-DTPA-octreotide should be limited to those cases in which other imaging techniques are inconclusive. ^{111}In-DTPA-octreotide is clearly more accurate for nonfunctioning paragangliomas of the head and neck, where MIBG scintigraphy usually fails.[123] In these patients, unexpected additional sites are frequently found. Unlike MIBG, ^{111}In-DTPA-octreotide lacks tissue specificity, providing information only on SS receptor status. Perhaps it can have a complementary role in metastatic tumors; in fact, some reports seem to indicate a higher sensitivity of SRS in detecting metastatic disease and in dopamine-secreting tumors when MIBG scintigraphy is negative, thus increasing diagnostic sensitivity.[123,124]

PET Radiopharmaceuticals

Several PET agents have been used or are under investigation for pheochromocytoma/paraganglioma, and they offer improved functional information. FDG, the only PET imaging agent that is widely available is not recommended for initial diagnosis since it is not specific; due its ability in identifying hypermetabolic lesions, it also depicts adrenocortical cancer and metastatic lesions.[125,126] Moreover, FDG has a limited sensitivity, approximately 70% for solitary benign or malignant pheochromocytoma; nevertheless, it has a role as an alternative modality when MIBG scintigraphy fails to image the tumor.[88,127] PET with ^{11}C-HED has been applied in patients with pheochromocytoma, allowing the visualization of both primary and metastatic deposits (90% sensitivity) within minutes of tracer administration, and has spatial resolution and a tumor-to-background ratio greater than ^{123}I-MIBG.[84] Also ^{18}F-DOPA and ^{18}F-FDA provide excellent imaging of paragangliomas and pheochromocytomas; diagnostic sensitivity is superior to FDG and specificity is similar to radioiodinated MIBG.[128] Thanks to the high spatial resolution of PET scanners, the recent introduction of hybrid machines (PET/CT) and to the selective tracer accumulation, very small lesions are detected and well localized; moreover, the lack of visible ^{18}F-DOPA uptake in normal adrenals makes image interpretation very easy.[95,111,128-130] In a recent study, ^{18}F-FDA localized the primary tumor and metastatic sites in all patients with pheochromocytoma, showing a large number of lesions not depicted with ^{131}I-MIBG.[90,131] Other advantages versus ^{131}I-MIBG scintigraphy are: less radiation exposure, no need of thyroid blockade, immediate imaging

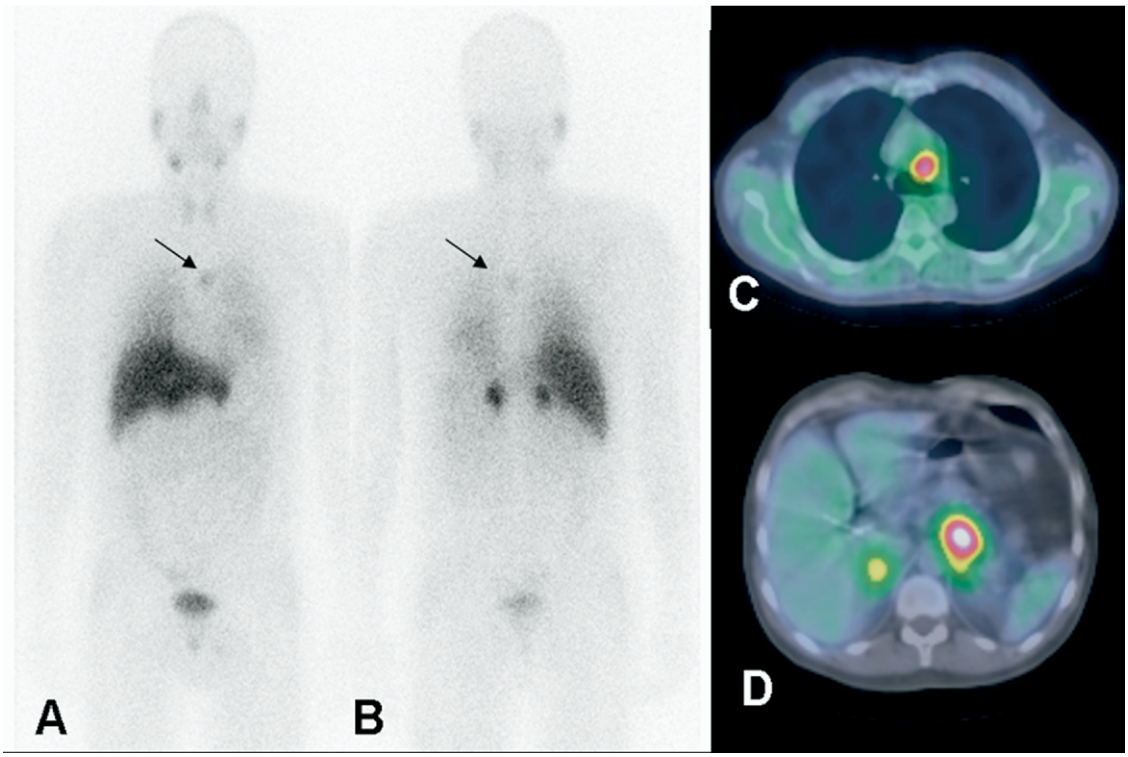

Figure 1 ^{123}I-MIBG scintigraphy performed in a hypertensive patient with bilateral adrenal pheochromocytomas. Anterior (A) and posterior (B) whole-body scintigraphy and fused SPECT/CT image (D) obtained with a hybrid machine clearly depict and correctly localize both pheochromocytomas. An unsuspected additional focus of uptake is seen in the thorax (arrow) and it is localized in the aortopulmonary window, as demonstrated by SPECT/CT image (C).

after injection. Unfortunately, ^{18}F-FDA currently has a high cost and limited availability. Recently, PET with ^{18}F-fluorobenzylguanidine has successfully localized pheochromocytoma in dogs.[132] Also octreotide analogs are under evaluation for somatostatin receptor imaging with PET or PET/CT, but more studies are needed (Fig. 2).

Neuroblastoma

Neuroblastoma (NB), which arises from precursors of the sympathetic nervous system, is the most common extracranial, highly malignant, solid tumor of childhood. NB has a strong propensity to metastasize to cortical bone, bone marrow, lymph nodes, and liver. Therefore, an accurate assessment of the extension of the disease is essential for the choice of treatment strategy as well as for prognostic evaluation; it requires CT (or MRI), bone scintigraphy, MIBG scintigraphy, bone marrow biopsies and urine catecholamine metabolites. Radiolabeled MIBG imaging is a well-established procedure in the diagnostic evaluation of NB, depicting primary and residual/recurrent NB, as well as metastatic lesions with an overall accuracy of about 90%.[9,133] The highest sensitivity (91-97%) is shown in the detection of bone deposits.[9] MIBG scan, performed at the time of diagnosis and after induction chemotherapy may have prognostic significance, as a positive scan during and after induction therapy suggests a poor outcome.[9,134] On the whole, MIBG imaging is today considered to be the most effective indicator of NB. Its major indications are: staging the disease at presentation and restaging after treatment; the search for postsurgical residual tumors; monitoring the effect of treatment; the early diagnosis of recurrence at follow-up.[135] Furthermore, it is essential as a prelude to ^{131}I-MIBG therapy. Currently, there is not a well-defined indication for radiolabeled SS analogs in children with NB due to the lower sensitivity of SRS than MIBG scan (64% versus 94%).[136,137] However, since in neuroblastoma SS receptors are associated with favorable clinical and biological prognostic factors,[43] ^{111}In-DTPA-octreotide scintigraphy could provide prognostic information; in fact a longer survival has been reported in patients with SS receptor-positive NB.[138]

PET imaging with ^{11}C-HED has been performed in patients with NB, giving high-quality functional images. However, when positive, the images are substantially equal to that of the MIBG scan.[86] FDG-PET can depict NB lesions and also those that fail to accumulate MIBG.[137] Recently, Kushner and coworkers[139] have proposed the use of FDG-PET combined with a bone marrow examination as the only imaging modality in the follow-up of patients at high risk of progressive disease. However, a major drawback of FDG-PET is the lack of visualization of skull lesions, because of high physiologic activity in the brain, with the underestimation of disease extension.[137] Therefore, in patients with NB, FDG-PET should be performed only if MIBG scintigraphy gives negative results. Also receptor imaging with PET/CT and ^{68}Ga-

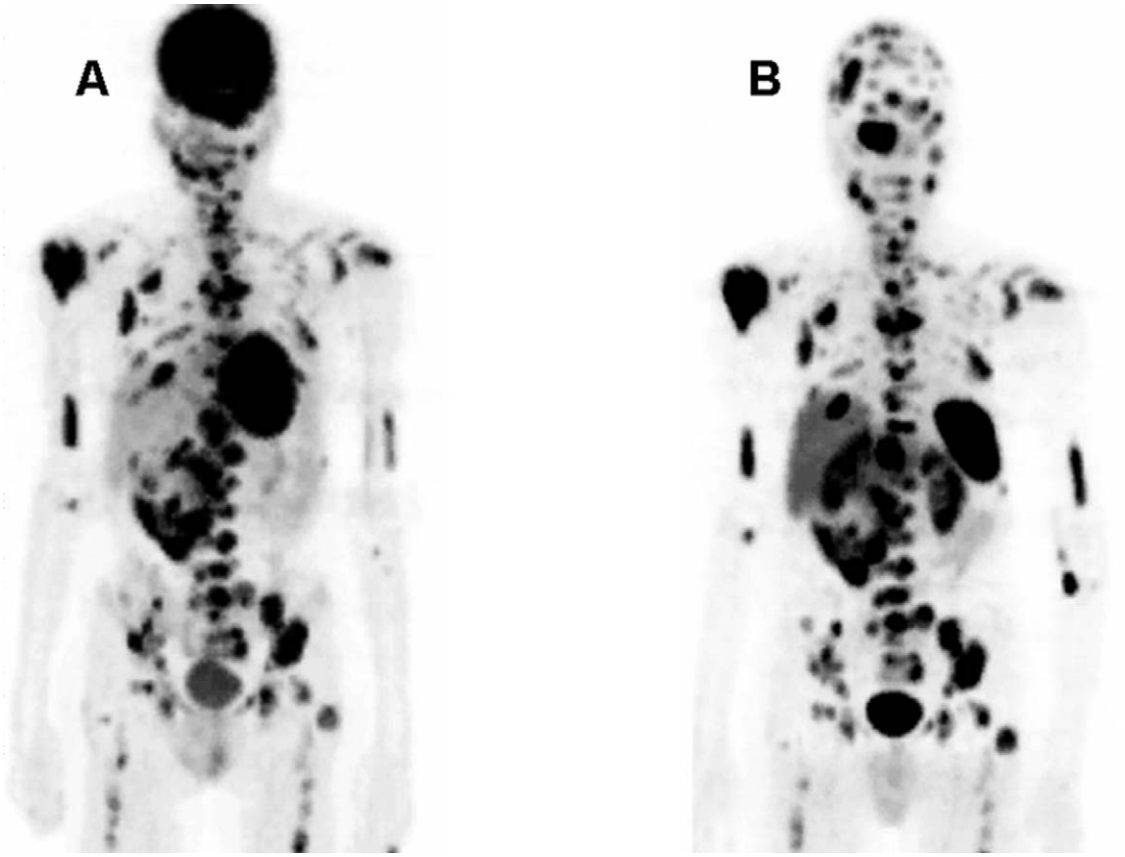

Figure 2 Comparison between FDG PET scans (A) and receptor PET (B) using ^{68}Ga-labeled DOTA-NOC performed in a 19-year-old neuroblastoma patient, showing high glucose metabolism and intense SS-receptor expression in the same lesions, ie, the primary tumor (arising from the right adrenal) and multiple bone metastases ("match" between FDG-uptake and SS receptor expression).

labeled peptides might be useful for evaluating neuroblastoma patients, but more studies are needed.

Neuroendocrine Tumors of the Gastrointestinal Tract

Clinical Presentation and Diagnosis

Neuroendocrine GEP tumors are rare neoplasms, representing approximately 2% of all malignant gastrointestinal tumors.[140] Classically, NETs of the gastrointestinal tract are classified into 2 main groups: (1) carcinoids, which are the most common and have been traditionally divided on the basis of their site of origin into foregut (lung, thymus, stomach and duodenum), midgut (distal ileum and proximal colon), and hindgut (distal colon and rectum) and (2) endocrine pancreatic tumors (EPTs), which are divided on the basis of hormone secretion and related clinical syndromes in functioning (ie, insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas) and nonfunctioning tumors, the latter representing approximately 15% to 30% of all EPTs. Gastrinoma is the prevalent type of EPT. With the exception of insulinomas, EPTs are malignant in most cases.[141] EPTs also can be part of MEN 1. A recent WHO classification proposed by Solcia and coworkers[2] classifies NETs of the gastrointestinal tract at the time of diagnosis, according to morphological and biological findings, with the aim of predicting tumor behavior and assessing the prognosis.[2] For each tumor site, the neoplasms are divided into three groups: well-differentiated tumors with either benign or uncertain behavior, low-grade malignancies and highly malignant tumors.[2,142]

Most NETs secrete a variety of peptide hormones and amines, which are valuable tumor markers both for diagnosis and follow-up. In addition, Chromogranin A, which is considered today the most important biochemical marker for NETs,[54,143] identifies tumors regardless of their location or their functional activity, with relatively high sensitivity. Diagnostic imaging modalities are used to detect and localize the primary tumor as well as in determining the extent of metastatic spread and tumor progression. However, tumor visualization by means of standard imaging modalities can be difficult, mainly because of the small size of the lesions, the presence of multiple tumor sites and the large variability in tumor location. For gastrointestinal carcinoids, endoscopy and endoscopic ultrasonography (US) provide sensitive tools for identifying gastric and intestinal lesions[144] whereas MRI and CT can efficiently visualize metastatic lesions. For endocrine pancreatic tumors, MRI as well as CT and endoscopic

US show less than optimal sensitivity, due to their small size. Currently, the most effective strategy to detect small pancreatic NETs seems to be intraoperative US.[145,146]

Radionuclide Imaging

Radiolabeled SS Analogs

Well-differentiated GEP tumors express SS receptors with high density and homogeneous distribution, as demonstrated by in vitro studies. Following the initial experience of the Rotterdam group,[147] in subsequent years SRS with ^{111}In-DTPA-octreotide has proved to be highly sensitive in detecting and localizing GEP tumors. When combined with SPECT, SRS is currently considered the first choice imaging modality and the most reliable staging procedure, with diagnostic sensitivity exceeding that of MRI and CT.[148] In GEP tumors, tumor visualization with SRS is irrespective of tumor site and hormonal secretion. In carcinoids SRS proved to be extremely useful for identifying the primary lesion and staging the disease, particularly for midgut carcinoids, with reported sensitivities varying from 80% to nearly 100%. Regarding EPTs, SRS is highly sensitive in detecting the primary tumor, with the only exception being insulinomas, which are less frequently imaged by SRS (<70% sensitivity) due to a lower incidence of SS receptors in general, and of the subtype 2 in particular.[58] In the presence of a pancreatic mass, a negative scan suggests a pancreatic adenocarcinoma or a poorly differentiated EPT. The best results of SRS are observed in gastrinomas; several studies have shown that SRS is more sensitive than all other conventional methods in localizing the primary tumor or identifying liver metastases. SRS can depict almost all tumors larger than 2 cm and 30 to 75% of gastrinomas smaller than 1 cm and, when combined with endoscopic US, will image more than 90% of EPTs.[149]

Beside the detection of the primary tumor and disease staging, further indications of SRS are: follow-up after operation; diagnosis of recurrences in case of increasing specific tumor markers; evaluation of response to treatment after chemotherapy or biological therapy (octreotide or interferon treatment); differential diagnosis of a NETs versus nonendocrine tumor in case of a space occupying mass, if a final diagnosis cannot be obtained by biopsy or operation. Another important role of SRS is the assessment of the receptor status of neoplastic lesions, to plan treatment with "cold" or radiolabeled somatostatin analogs. Finally, the use of an intraoperative γ-probe after ^{111}In-octreotide injection can be of help in detecting very small primary tumors or metastases, and to confirm a complete resection.[150,151]

SRS changes patient management in 17 to 28% of patients with GEP tumors[152-154] and in 47% of patients with gastrinoma[155] by identifying previously unrecognized lesions or clarifying equivocal results obtained by other imaging modalities. Moreover, SRS may prevent surgery in patients with metastatic lesions not detected by conventional imaging[55,156] and this benefit outweighs the high cost of SRS. The diagnostic accuracy of SRS may further increase with the use of combined SPECT/CT devices.[157] In the experience of Krausz and coworkers,[158] SPECT/CT can improve SRS image interpretation, allowing the precise anatomic localization of scintigraphic findings in 32% of patients studied, and changing patient management in 14% of cases.

The ^{99m}Tc-labeled SS analog depreotide (^{99m}Tc-P829) has shown high sensitivity and specificity in the evaluation of solitary pulmonary nodules, including small cell lung carcinomas[159]; however, when compared with Octreoscan, ^{99m}Tc-P829 yields a far lower detection rate for NET, especially for liver metastases.[160] Among ^{99m}Tc-labeled somatostatin analogs, ^{99m}Tc-EDDA-hydrazinonicotinyl-Tyr^3-octreotide (^{99m}Tc-EDDA-HYNIC-TOC) is the most promising agent with clear advantages over ^{111}In-DTPA-octreotide such as an improved image quality especially with SPECT (Figs. 3 and 4), lower radiation dose, 1-day protocol and daily availability.[36] Similar to previous reports,[161] Gabriel and coworkers[162] report an overall sensitivity of 80%, a specificity of 94.4% and accuracy 82.9% in patients with GEP NETs.

Radiolabeled MIBG

This radiopharmaceutical plays a more limited role in carcinoids when compared with pheochromocytoma/paraganglioma and neuroblastoma. A review of the series reported in literature shows that approximately 70% (40-85%) of carcinoids are able to concentrate MIBG.[9,109,163-165] Primary and residual tumors are sometimes visualized, but the most striking imaging is that of carcinoid metastases in the liver, provided that SPECT with ^{123}I-MIBG is performed.[163,164] When radioiodinated MIBG and SRS results in carcinoids are compared, SRS shows a much better sensitivity (>80%) in detecting both primary and metastatic lesions.[163-169] Also, when single lesions are analyzed, SRS shows a higher sensitivity for localization of the primary tumor and extra-hepatic abdominal lesions as well as ocular,[170] thoracic and bone involvement, while similar diagnostic results have been reported when liver metastases are concerned.[164] There are occasional reports of MIBG uptake in lesions from carcinoid tumor not visualized by somatostatin receptor scintigraphy.[163,164,169]

PET Tracers

FDG frequently fails to visualize tumors with a low proliferation rate like many GEP tumors have (Fig. 5).[77,81] In fact, an intense FDG uptake frequently is observed in those GEP tumors that show an aggressive clinical behavior.[80] Adams and coworkers[171] compared the results of FDG-PET with those of SRS and with the expression of Ki-67, and found that FDG uptake increased only in GEP tumors with high Ki-67 immunoreactivity, indicating a high proliferation rate and a poor prognosis, whereas SRS was negative. Therefore, FDG has a prognostic significance and can direct a therapeutic decision. According to the recent experience of Baum and coworkers (unpublished results), FDG-PET/CT and ^{68}Ga-DOTA-NOC PET/CT in the same patient frequently revealed a "flip-flop pattern," ie, that FDG positive lesions are receptor negative and vice versa (similar to the behavior of FDG in differentiated thyroid cancer). However, sometimes also very slowly progressive NETs show intense FDG uptake.

A peculiar characteristic of GEP NETs is the uptake and decarboxylation of L-DOPA and 5-HTP, transforming them into biogenic amines such as dopamine and serotonin. This property

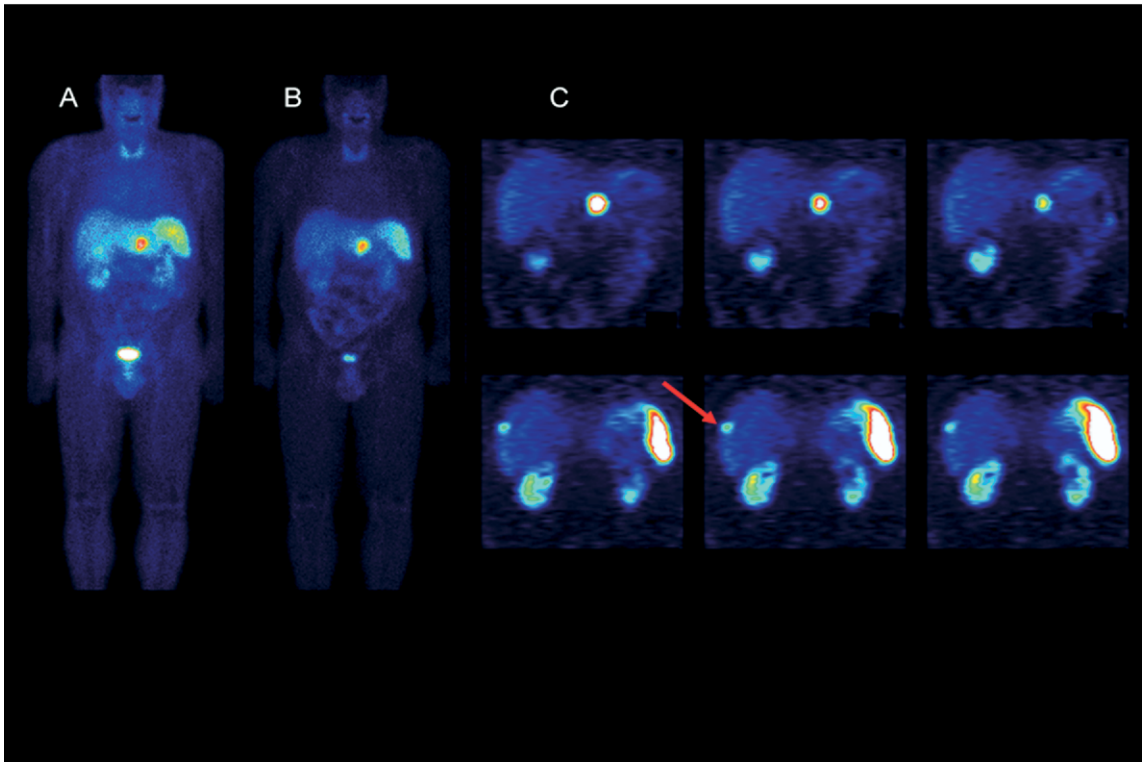

Figure 3 Whole-body scintigraphy, anterior views performed 1 hour (A) and 4 hours (B) after injection of ^{99m}Tc-EDDA-HYNIC-TOC: intense SS receptor expression in a neuroendocrine pancreatic carcinoma; no metastases are seen on the planar views. Coronal SPECT slices (C) enable the detection of a small liver metastasis (8 mm in diameter, as confirmed by surgery; arrow).

has been used for imaging GEP tumors with ^{11}C- or ^{18}F-labeled L-DOPA or ^{11}C-labeled 5-HTP. In the experience of Orlefors and coworkers, [98] ^{11}C-5-HTP can image tumor lesions in 95% of patients and shows a higher sensitivity (84%) when compared with SRS (47%) and CT (42%) for imaging small NET lesions such as primary tumors; it can also be helpful for evaluating the metabolic effects of treatment, which are not obtained with other imaging modalities.[55,96-98,172] However, this functional approach may yield false-negative results in detecting undifferentiated carcinoids. Quantitative evaluation of PET with ^{11}C-5-HTP in treatment monitoring of NETs has shown a high correlation (>95%) between the uptake of ^{11}C-5-HTP and changes of 5-hydroxy-indol-acetic acid levels.[96]

^{18}F-DOPA can be used to visualize carcinoids and its sensitivity exceeds that of SRS, conventional morphological imaging, and FDG for detecting primary tumors and lymph node metastases.[173,174] Correlation of ^{18}F-DOPA results with immunohistochemical data show that most false-negative PET findings occur in patients with nonserotonin-expressing tumors.[173]

Increasing data are available concerning PET with radiolabeled SS analogs such as ^{64}Cu-TETA-OC, ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE, all showing very promising results.[13,100,175,176] Recently, in a large group of patients (more than 750 studies in more than 250 patients studied before and after peptide receptor radionuclide therapy) with various NET, Baum and coworkers reported a very high diagnostic accuracy of ^{68}Ga-DOTA-NOC PET/CT, which by far surpassed the sensitivity of ^{99m}Tc-EDDA-HYNIC-TOC or ^{111}In-octreotide SPECT in detecting metastatic lesions.[49] ^{68}Ga-DOTA-NOC receptor PET/CT shows much higher sensitivity especially for detecting bone metastases as well as liver and small lymph node lesions, and is able to reveal the primary tumor in many patients with unknown primary tumor presenting mainly with known hepatic metastases (Figs. 6 and 7). In a smaller series of patients, Öksüz and coworkers compared ^{68}Ga-DOTA-TOC PET/CT and ^{111}In-Octreoscan SPECT/CT and found additional metastases in 24 of 36 patients (67%) and a more precise localization of lesions with PET/CT.[177]

Ectopic ACTH-Secreting Tumors

Ectopic ACTH secretion (EAS) accounts for approximately 10% of cases of Cushing's syndrome; it may be associated with either highly malignant tumors, mainly small cell lung cancer (17.5% of cases) or with less aggressive NETs, mainly bronchial carcinoids (30% of cases)[178]; other NETs that may be less frequently responsible for EAS are thymic carcinoids, GEP tumors, pheochromocytomas, and medullary thyroid carcinomas.[179] Localization of the tumor by conventional imaging is challenging. CT and MRI are used most frequently to localize the source of EAS; however, the tumor cannot be found in a significant number of cases (12-19% in recent studies) because of the small size, despite repeated imaging evaluation and prolonged follow-up.[178,179] Among nuclear

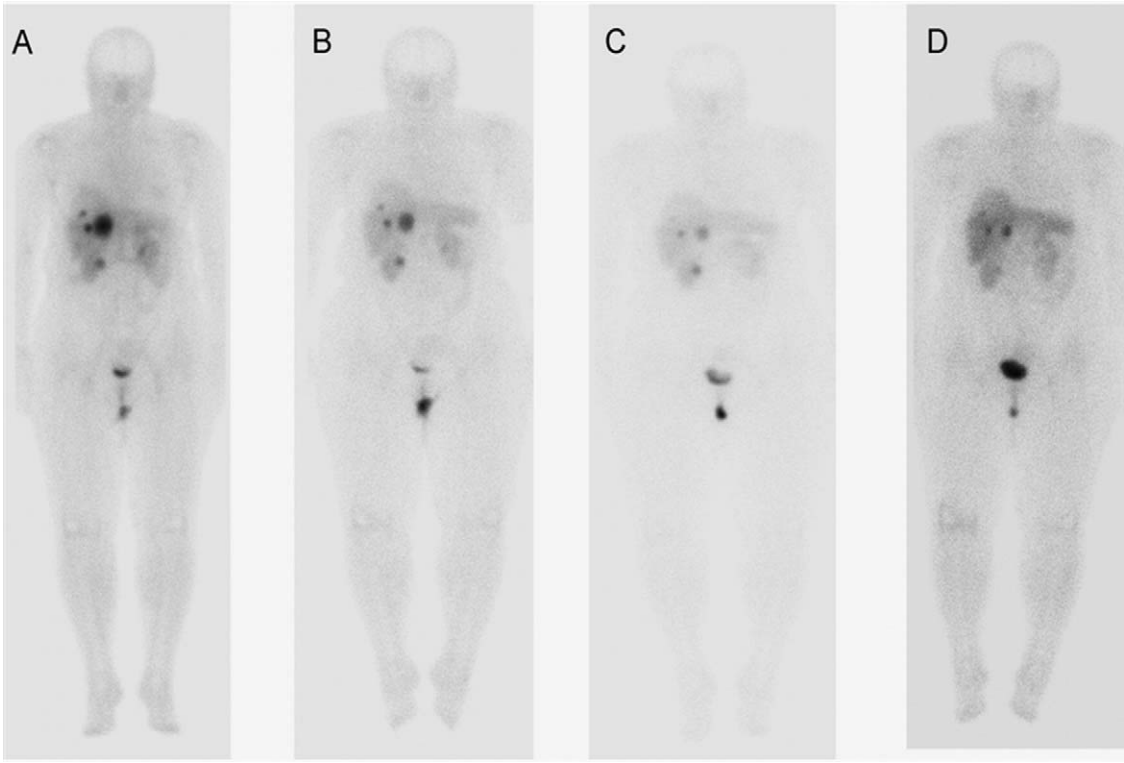

Figure 4 Liver metastases of a neuroendocrine pancreatic carcinoma (glucagonoma) before (A) and after (B-D) multiple peptide receptor radionuclide therapies using the somatostatin analog ^{90}Y-DOTA-TATE. Whole-body scans (anterior views) using ^{99m}Tc-EDDA-HYNIC-TOC show a continuous decrease of uptake and size of the liver lesions.

medicine techniques, SRS has been proposed to localize ectopic ACTH secreting tumors; however, published studies report discordant results.[180] In a recent prospective study by Pacak and coworkers, SRS detected ectopic ACTH secreting tumors as well as CT (53% sensitivity for both techniques) and better than MRI (37% sensitivity) and FDG-PET (35% sensitivity) and seems to have a complementary role, mainly when CT or MRI results are equivocal.[181] Additionally, when SRS with standard injected activity (ie, 200 MBq) is negative, a repeated SRS with a higher dose may occasionally localize the tumor.[181] Controversial results are reported also with FDG-PET,[181,182] even though in individual cases it may be a useful tool when the tumor is not detectable with other imaging modalities.[183] All the tracers used for PET in NET such as ^{11}C-5-HTP, ^{18}F-DOPA, ^{18}F-FDA, ^{68}Ga-DOTA-TOC, and ^{68}Ga-DOTA-NOC may potentially be useful to localize ectopic ACTH secreting tumors. Eriksson and coworkers reported positive results with ^{11}C-5-HTP in 3 of 5 patients with ACTH-producing foregut carcinoids.[82]

Medullary Thyroid Carcinoma

Clinical Presentation and Diagnosis

Medullary thyroid carcinoma (MTC) is a NET originating in the parafollicular cells (C cells) of the thyroid, which derive from the neural crest and secrete calcitonin as well as other polypeptides such as carcinoembryonic antigen (CEA), VIP and SS. The reported prevalence is 3 to 12% of thyroid cancers. MTC may occur in either sporadic (75-80% of cases) or inherited forms (20-25%). It is often invasive and progressive with high potential of metastases.[184] Nuclear medicine procedures, although having a minor role in the preoperative evaluation of MTC, are essential in the postoperative follow-up. Patients with postoperative normal levels of calcitonin and CEA are considered surgically cured.[185] However, despite aggressive surgery, about 50% of patients with MTC develop a recurrence which is usually difficult to localize, even with high resolution diagnostic imaging; this is particularly true for liver metastases which tend to be miliary and are identified only with selective venous sampling catheterization or angiography.[186-188]

Radionuclide Imaging

Because of the diagnostic difficulties in localizing MTC lesions, numerous radiopharmaceuticals have been proposed, some of them having also a therapeutic role.[189-191]

Radiolabeled MIBG

After the first encouraging reports with positive MIBG scintigraphy in MTC patients, rather disappointing results followed.[192,193] Specificity is high (>95%), but sensitivity is only approximately 30% and does not seem to improve with the use of ^{123}I-MIBG and SPECT.[190] This inconsistent depiction of MTC lesions may be due to the histologic heterogeneity of MTC and/or the possible anaplastic transformation of the metastases.[9] However, MIBG uptake has been found to be

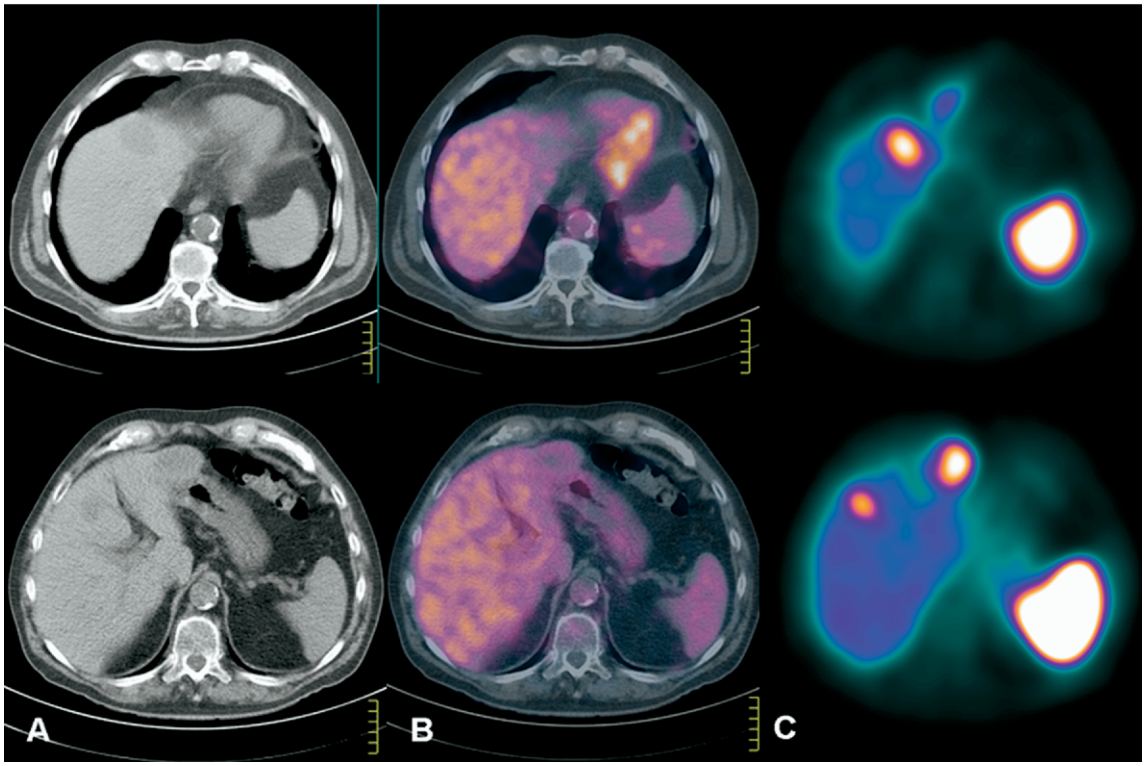

Figure 5 Liver metastases from a carcinoid in the ileum (A, transversal CT slices; B, fused images FDG-PET/CT; C, transversal SPECT images with ^{111}In-DTPA-octreotide), which are well depicted at SRS and show no FDG uptake ("mismatch" between FDG uptake and SS receptor expression).

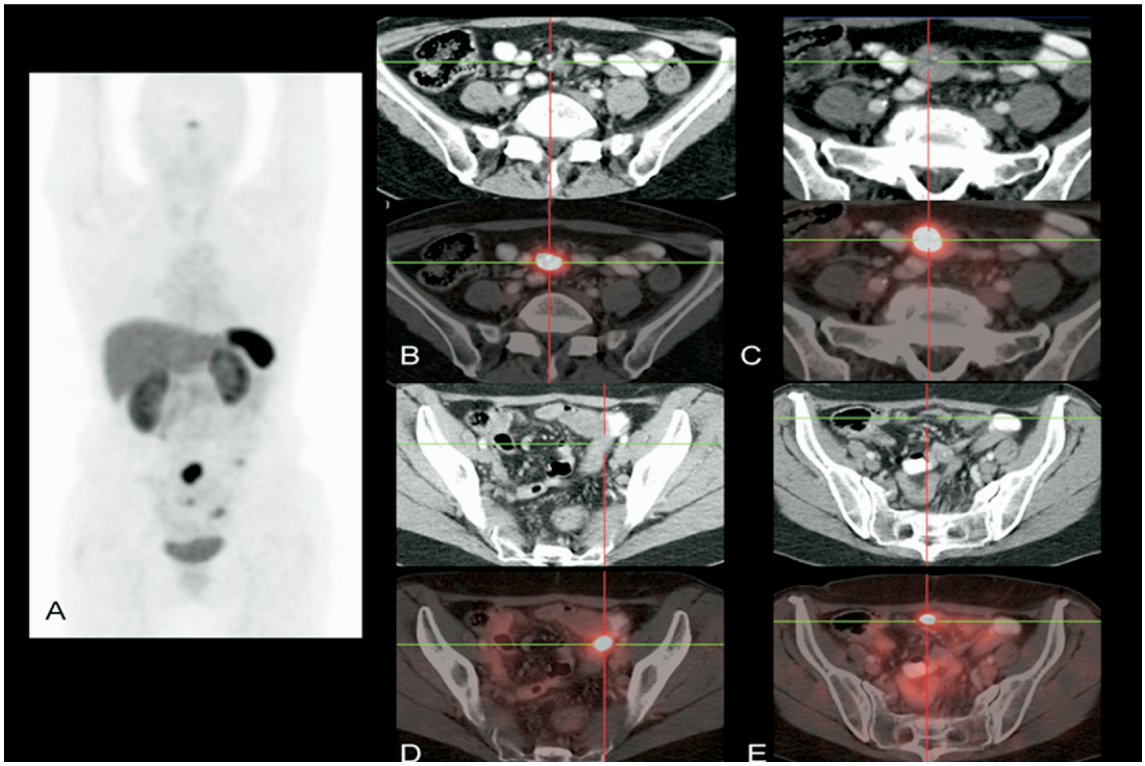

Figure 6 ^{68}Ga-DOTA-NOC PET/CT in a patient with multiple NETs of the ileum and colon (maximum intensity projection image) (A), and selected transversal slices (B-E) with the corresponding CT slices and fused images) showing the multiple primary tumors and peritoneal carcinosis.

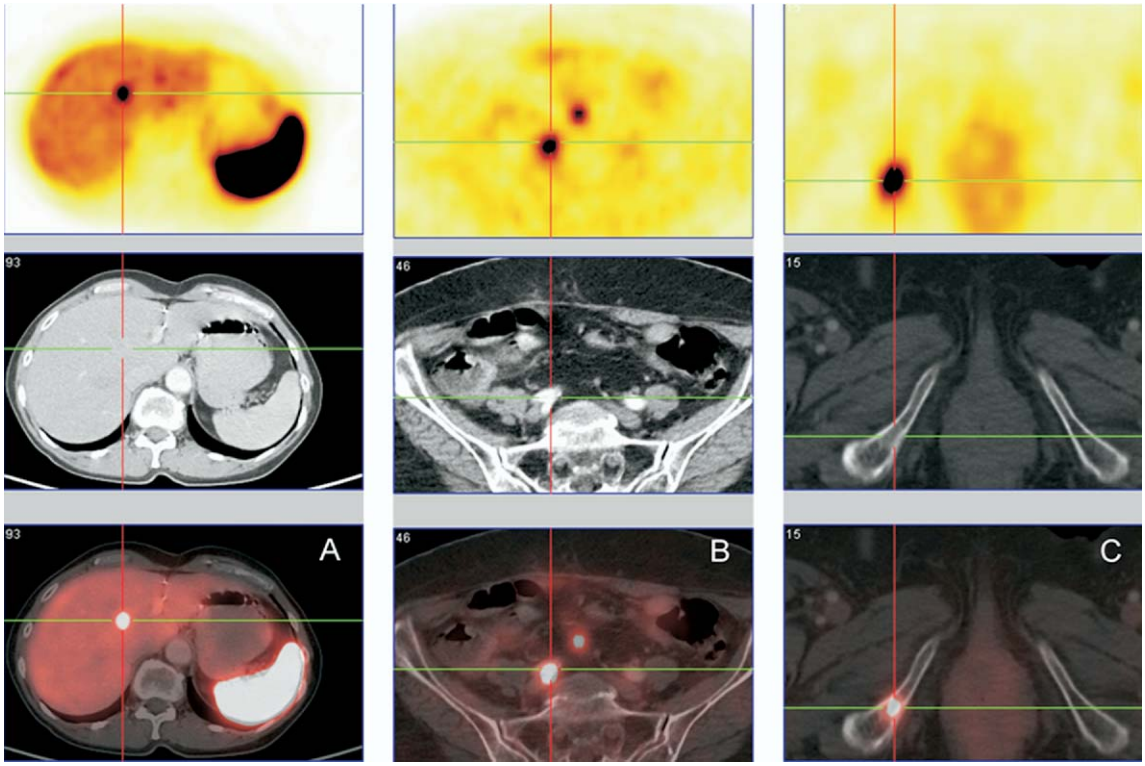

Figure 7 Small liver metastasis (A), not seen on contrast-enhanced (portal-venous phase) CT scan as well as small lymph node (B) and bone (C) metastases as detected by ^{68}Ga-DOTA-NOC receptor PET/CT.

high enough in some patients to attempt MIBG therapy.[109,190] In MTC, the utility of MIBG scintigraphy mainly resides in locating adrenal medulla hyperplasia or pheochromocytoma in MEN syndromes and in the evaluation of MIBG uptake in known lesions as a prelude to ^{131}I-MIBG palliative therapy.[190]

Radiolabeled SS Analogs

The reported results of ^{111}In-DTPA-octreotide scintigraphy are extremely variable. Those of Baudin and coworkers are disappointing, reporting a poor sensitivity (37%), which is lower than conventional imaging, whereas those of Dörr and coworkers are definitely favorable, especially for the detection of occult lesions.[194,195] False-positive results with ^{111}In-DTPA-octreotide are possible; a diffuse mediastinal uptake may be seen after external beam radiation therapy to the neck and mediastinum, as a result of postradiation pulmonary fibrosis.[196]

In a study of Papotti and coworkers,[197] who analyzed the distribution of the 5 SS receptors by immunohistochemistry, MTC displayed a heterogeneous expression of receptor subtypes. This finding has clinical implications because those patients whose lesions do not express sstr2 or sstr5 cannot be imaged by SRS nor treated with ^{90}Y-DOTA-TOC. In these patients, MIBG scan may be positive, potentially offering a therapeutic option with this agent.[164,198] The result of ^{111}In-DTPA-octreotide scintigraphy also may have prognostic significance. In vitro studies have shown that the incidence of SS receptors is directly correlated with tumor differentiation.[199] In vivo studies have shown high sensitivity of ^{111}In-DTPA-octreotide for cervical and upper mediastinum lymph nodes in patients with occult disease, which is typically associated to a less aggressive behavior of the tumor.[196] On the contrary, SRS is less sensitive in patients with distant metastases and progressive disease.[200]

Other radiopharmaceuticals, ^{99m}Tc(V)-DMSA (no longer commercially available),[193] radiolabeled anti-CEA antibodies[200,201] or anticalcitonin or antichromogranin A monoclonal antibodies,[202] and the recently developed cholecystokinin-B/gastrin-related peptides[67] and ^{99m}Tc-EDDA/HYNIC-TOC[203] seem to show considerable sensitivity but are still considered experimental investigations.

PET Radiopharmaceuticals

A number of patients with MTC have been studied with PET. Recent reports seem to indicate a higher lesion detection efficacy of FDG-PET when compared with scintigraphic studies with single-photon emitters.[204-207] Szakall and coworkers, who studied patients with elevated levels of calcitonin after surgery, reported a higher sensitivity of FDG-PET than CT and MRI, especially in detecting cervical, supraclavicular and mediastinal lymph nodes, with a detection rate of 95%, but failed to detect small lesions in the lung and liver.[205] However, other studies showed a lower sensitivity of FDG-PET in comparison to CT.[94,208,209] FDG uptake in MTC seems to be associated with poor differentiation and high proliferative activity, as demonstrated by rapidly increasing CEA levels and immunoreactivity for Ki-67 expression in surgically removed lesions (Fig. 8).[171]

^{18}F-DOPA is also used in patients with MTC; when compared with the results of FDG-PET, SRS, and CT or MRI,

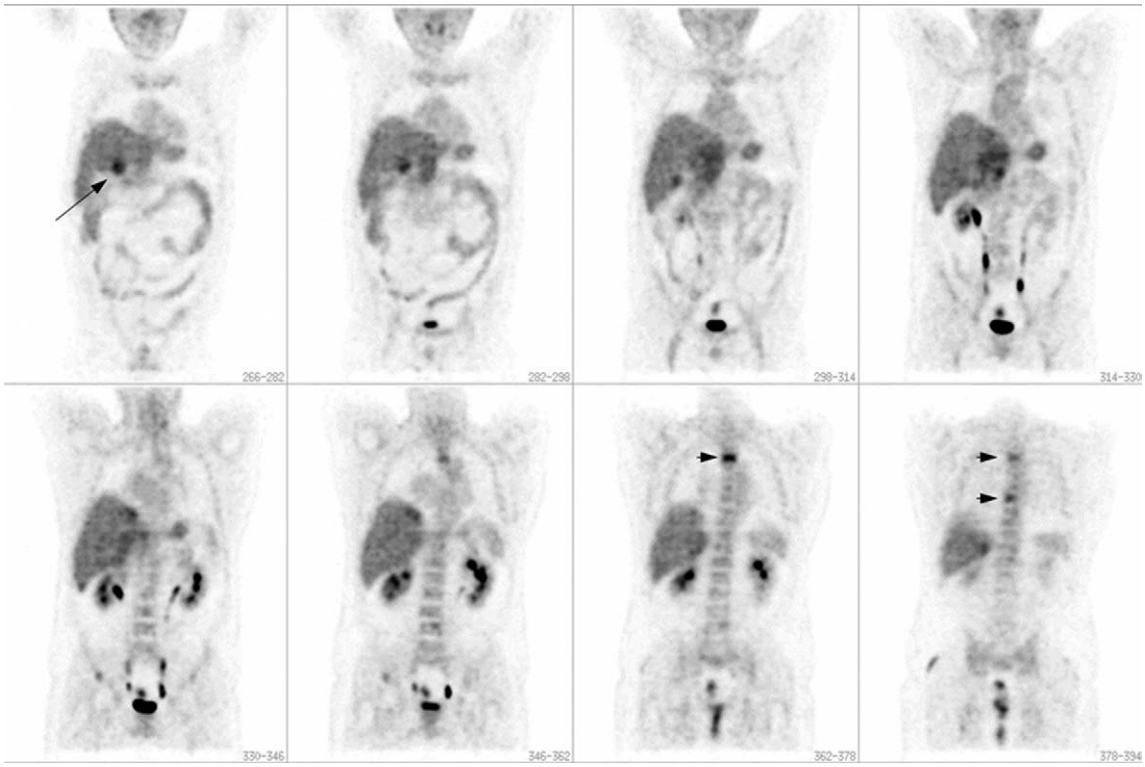

Figure 8 FDG-PET performed in a 62-year-old man during follow-up after total thyroidectomy for MTC, because of increased plasma levels of calcitonin. Coronal views showing FDG uptake in a liver metastasis (arrow) and in bone metastases in the spine (arrowheads).

^{18}F-DOPA proved to have lower sensitivity, especially for liver metastases but higher specificity for the detection of lymph node involvement and loco-regional relapses.[94]

Recently, ^{68}Ga-labeled SS analogs like DOTA-TOC or DOTA-NOC have been used in MTC patients, mainly for evaluating the receptor density before peptide receptor radionuclide therapy with Lu-177 or Y-90 labeled DOTA-TATE.[210]

In conclusion, radiopharmaceuticals for the diagnosis of NETs, ie, ^{131}I-MIBG for pheochromocytomas, paragangliomas and neuroblastomas, and ^{111}In- or ^{99m}Tc-labeled somatostatin analogs for NETs of the gastrointestinal tract, have become an invaluable tool for the management of neuroendocrine tumors and are extensively used in routine clinical practice because of their capability to detect abnormalities before morphological changes occur. This functional information complements that of morphological imaging techniques, such as ultrasounds, computed tomography and magnetic resonance. Significant improvements have been made by the introduction of hybrid machines, such as SPECT/CT or PET/CT that allow one to perform whole-body imaging quickly and with high anatomical resolution. Moreover, the development of more specific radiopharmaceuticals which are selectively taken up by the tumors provide excellent quality images with high contrast, allowing to depict very small lesions and making them easy to interpret. In the management of NETs, the contribution of nuclear medicine is essential in several clinical settings, such as initial diagnosis and disease staging, follow-up, treatment planning and treatment monitoring. In addition the tracer uptake might be used as a prognostic parameter and as a predictor of treatment response. A more extensive use of ^{68}Ga-DOTA-coupled peptides will further enhance the value of nuclear medicine procedures both in diagnosis and in therapy, especially for their potential role in pretherapeutic evaluation before peptide receptor radionuclide therapy. The different uptake patterns observed with the various tracers available might reflect different structural or ultrastructural characteristics, which can be imaged and differentiated by radiotracers. Therefore, scintigraphic imaging may help stimulate further research to broaden knowledge of the most intimate structure of neuroendocrine tumors.

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