# 18 Receptor PET/CT Imaging of Neuroendocrine Tumors

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This chapter is dedicated to Gustav Hör, Professor Emeritus and former Director of the Department of Nuclear Medicine, University of Frankfurt/Main, on the occasion of his 75th birthday.

## 18.1 Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms which are characterized by their endocrine metabolism and histology pattern. The diversity of NETs can be judged with the different names [carcinoid tumor, APUDoma gastroenteropancreatic (GEP) tumor, islet cell tumor, neuroendocrine tumor, and neuroendocrine carcinoma] that have been put forward for describing these endocrine tumors (Solcia et al. 2000). Oberndorfer (1907) first described the term "carcinoid tumor" for the "endocrine tumor originating in small intestine and characterized by slow growth and late metastases". Previously, NETs have also been called APUDomas (for amine precursor uptake and decarboxylation) and were suspected of originating from the neural crest. However, the peptide-secreting cells of the tumors are not derived from the neuroectodermal unit (Jensen 2005). Subsequently, the origin of these tumors was traced to pluripotent stem cells or differentiated neuroendocrine cells (Li and Beheshti 2005). The slow growth of these tumors makes it very difficult to localize the site of the tumor in the early stage (Baum and Hofmann 2004; Kaltsas et al. 2004). Localization is essential to select the optimal currently available management protocols (including curative surgery, cytoreductive surgery, and antiproliferative tumor treatment) and for predicting the patient's prognosis (Jensen 2005). The various compounds produced by these tumors, along with their characteristic symptoms – although useful in the diagnosis of the disease – do not help much in solving a clinician's dilemma to decide upon the best treatment regime. Conventional imaging modalities such as ultrasonography (USG), CT scan, magnetic resonance imaging (MRI), although useful for detecting the number of lesions and other anatomical details, do not give information on the functional status of the tumor, which is essential for defining the prognosis (Li and Beheshti 2005).

These issues and the discovery of overexpression of receptors for peptide hormones in cancerous tissue in the mid 1980s led to the gradual upsurge in the role of nuclear medicine procedures in the diagnostic algorithm for NET. The biokinetics of peptides, unlike radiolabeled monoclonal antibodies, are favorable because of fast clearance, rapid tissue penetration and low antigenicity (Krenning et al. 2004). Many different radiolabeled peptide analogs, for example, somatostatin, cholecystokinin (CCK), bombesin, substance P, gastrin, vasoactive intestinal peptides (VIP), and neuropeptide (NP)-Y have been used for the evalu-

ation of receptor expression on tumor cells (Behr and Behe 2002; Behr et al. 1998, 2001; Blum et al. 2000; Krenning et al. 1989, 1992, 1993; Kwekkeboom et al. 2000; Reubi et al. 1997, 2000a, 2001a, 2002; van Hagen et al. 1996; Virgolini et al. 1995, 1996, 1998; Weiner and Thakur 2002). Amongst the somatostatin analogs, 111In-DTPA-octreotide (DTPA-OC) was approved by the Food and Drug Administration (FDA) for scintigraphy of patients with neuroendocrine tumors. Various other radiopharmaceuticals have been used successfully for the diagnosis of NET, especially metastasized NETs. This article will focus mainly on the role of receptor PET and PET/CT along with different peptides currently used in the diagnosis of NET. The clinical symptoms and the role of other diagnostic modalities (conventional imaging as well as basic nuclear medicine procedures) will be highlighted briefly.

## 18.2 Pathology and Clinical Course of NETs

The incidence of neuroendocrine tumors is reported to be low; however, because of the indolent nature of the tumor, it is expected that many of the patients do not get diagnosed during their lifetime. Although NET can occur at many places in the body, the most common sites are the bronchus/lungs and the gastroenteropancreatic tract; other less common sites are skin, adrenal glands, thyroid, and genital tract (Jensen 2005). The definition of NET encompasses a wide variety of tumors, for example, gastroenteropancreatic NETs (GEPs), neuroblastoma, multiple endocrine neoplasia (MEN), pheochromocytoma, medullary thyroid carcinoma, small cell lung cancer, and others. Traditionally, NETs are classified according to the site of origin (foregut, midgut, and hindgut) as the tumors originating from the same site share functional manifestations, histochemistry, and secretory granules (Jensen 2005). Based upon histopathology, WHO has defined a separate classification to the NETs (Schmitt-Gräff et al. 2000; Solcia et al. 2000). Approximately 70% of carcinoid tumors originating from GI tissue are found in the following three sites: bronchus, jejunoileum, or colon/rectum. The carcinoid tumors and other tumors originating from the pancreas commonly show a malignant behavior. Other than insulinomas, in which fewer than 10% are malignant, nearly 50%–100% of pancreatic NET show a malignant behavior. Among the NETs of the GI tract, the incidence of metastases is highest in jejunoileum (58%), followed by lung/bronchus (6%) and rectum (4%) (Jensen 2005).

NETs consist of monotonous sheets of small round cell nuclei and are characterized by their propensity to being stained with silver and to markers of neuroendocrine tissues (e.g., chromogranin, neuron-specific enolase, and synaptophysin) using immunohistochemical methods. On electron microscopy, these tumors possess numerous membrane-bound neurosecretory granules containing various hormones and biogenic amines. The secretion of these into the blood gives rise to various typical clinical syndromes (Jensen 2005).

NETs have also been classified according to the presence or absence of clinical syndromes into functional/nonfunctional NETs (Jensen 2005). Nonfunctional NETs comprise nearly 33%–50% of all NETs. The symptoms present in this subset of patients with a NET are largely related to the mass effect of the tumor. Many times they are detected occasionally, often at a late stage when the tumor is already metastasized. In the group of functional NETs, the most common symptoms are diarrhea, flushing, pain, asthma/wheezing, pellagra, carcinoid heart disease such as endocardial fibrosis (Jensen 2005). There are numerous factors that influence the survival and prognosis of the patients among which the presence of liver metastases is the single most important factor. A correlation has been found between the size of the primary tumor and the chances of metastases in small intestinal carcinoids. Metastases to liver occurred in 15%–25% of tumors if the tumor diameter was smaller than 1 cm, in 58%–80% if it was 1–2 cm, and in more than 75% if the tumor size was larger than 2 cm (Jensen 2005). All these factors make it essential to have a correct diagnostic algorithm before selecting a particular treatment regime.

## 18.3 Diagnosis

The diagnosis of NET begins with a detailed history and thorough clinical examination. The characteristic history of flushing and intractable diarrhea warrants biochemical evaluation, which starts with measuring serum serotonin or the metabolite in the urine (5-hydroxy indole acid). Other NET markers, such as chromogranin A and neuron-specific enolase (NSE), are measured in serum. Generally these markers are elevated in carcinoid tumors. In case gastrinoma is suspected (history of abdominal pain, diarrhea, and gastroesophageal reflux disease), the fasting gastrin level should be measured. If the diagnosis of insulinoma is suspected, elevated insulin levels are found in fasting condition. C-peptide and serum glucose levels are also measured. In case pheochromocytoma is suspected, metanephrines, catecholamines, and their metabolites should be measured in the blood and urine (Jensen 2005).

After the evaluation of biochemical markers, the next step in the diagnostic algorithm is to determine the site of the primary tumor. Chest x-ray should be performed specifically if a thoracic origin of the tumor is suspected (Bombardieri et al. 2004). The role of USG in diagnosis of NET is variable and depends largely on the site of disease. USG has very high diagnostic accuracy for detection of liver metastases. If a gastric or pancreatic primary tumor is suspected, endoscopic USG should be used. Sometimes, for assessment of tumor vascularity, color Doppler and power Doppler USG are used in conjunction with CT.

CT and MRI are used for morphologic delineation of the tumor. CT is essential for preoperative staging. It is also used in patient follow-up. The accurate measurement of tumor size and extent can be evaluated using three-dimensional reconstruction. MRI is the method of choice in the study of cervical masses. MRI is also useful in intracranial lesions, intraspinal lesions and for detection of bone marrow involvement (Bombardieri et al. 2004). However, in spite of giving a perfect anatomical information of the tumors, these morphologic imaging methodologies are of limited use for determining the functional tumor status. This is the field where nuclear medicine procedures, with its armamentarium of radiopharmaceuticals, yields essential information in addition to morphological parameters. One significant advantage of nuclear medicine imaging techniques is the possibility of performing a whole-body scan in a single study.

## 18.4 Radionuclide Imaging of NETs

Radionuclide imaging has been used for the diagnosis of NET for many years. However, only in the last decade, PET and PET/CT, using specific radiopharmaceuticals, have gained a special role in the diagnostic work-up of NET patients.

### 18.4.1 Radiopharmaceuticals Used in Conventional Nuclear Medicine

#### 18.4.1.1 $^{131}$I-MIBG and $^{123}$I-MIBG

Metaiodobenzylguanidine (MIBG), a functional and structural analog of norepinephrine, tagged with the gamma-emitting radionuclide $^{123}$I or $^{131}$I, is used to localize neuroblastomas, pheochromocytomas, and paragangliomas (Berglund et al. 2001; Castellani et al. 2000; Shapiro et al. 1985, 1989). $^{123}$I is preferred over $^{131}$I because of the better physical characteristics, higher photon efficiency, and the possibility of performing a high-quality SPECT study. The tumor uptake of MIBG is inhibited by several drugs such as tricyclic antidepressants, sympathomimetics, and certain antihypertensive/cardiovascular drugs which must be paused prior to imaging with $^{123}$I-MIBG or $^{131}$I MIBG (Khafagi et al. 1989; Solanki et al. 1992).

##### *Peptide-Based Radiopharmaceuticals for Diagnosis of NETs*

Radiolabeled peptides have been used for targeting specific receptors on neuroendocrine tumors or over 15 years now (Krenning et al. 1989, 1990, 1992). The overexpression of peptide receptors in various tumor cells opened a

new chapter in the field of molecular imaging. Peptides have better pharmacokinetic properties and no (or very low) antigenicity as compared to monoclonal antibodies, making them an ideal ligand for receptor-based scintigraphy. Somatostatin, a cyclic peptide hormone, or somatostatin analogs labeled with different radionuclides, is an example of these peptides that have been used with high efficiency in the diagnosis of NETs.

#### 18.4.1.2 Somatostatin Receptor-Based Peptides

There are two naturally occurring bioactive forms of somatostatins: somatostatin-14 and somatostatin-28. The receptors of somatostatin are normally expressed in different parts of the body (e.g., in the pituitary, thyroid gland, pancreas, and GI tract). The primary action of this peptide hormone is the inhibition of hormone secretion and modulation of neurotransmission and cell proliferation through specific G-protein-coupled receptors (Wild et al. 2003). Five different types of somatostatin receptor proteins have been cloned (sstr1–5). Some of these receptors are overexpressed in NETs, which enables their visualization and localization with radiometal chelator conjugates of somatostatin analogs (Wild et al. 2003). Most of the tumors that have been studied with radiolabeled somatostatin analogues mainly express sstr2; however, recent results have shown that sstr1 and sstr3–5 are also expressed on many tumors to varying degrees (Reubi et al. 2001b). In neuroendocrine tumors of mid-gut origin, sstr2 is expressed maximally (95%) followed by sstr1 (80%) and sstr5 (75%) (Jensen 2005). The first radiolabeled somatostatin analog to be approved for the scintigraphy of NET was $^{111}$In-DTPA- D-Phe1-octreotide (OctreoScan, $^{111}$In-pentetreotide) (Krenning et al. 1989, 1990, 1992). Results have shown that this radiopharmaceutical is ideally suited for localizing primary and metastatic NET (Krenning et al. 1993; Lebtahi et al. 2002). The $^{99m}$Tc-labeled somatostatin analogs such as $^{99m}$Tc-depreotide, $^{99m}$Tc-vapreotide, $^{99m}$Tc-P829, and $^{99m}$Tc-EDDA-HYNIC-TOC are also used (Decristoforo et al. 2000; Lebtahi et al. 2002; Virgolini 2000). $^{99m}$Tc-EDDA-HYNIC-TOC (Fig. 18.1) has been shown to be superior to $^{111}$In-pentetreotide for the detection of sstr-positive tumors (Decristoforo et al. 2000). In an effort to find somatostatin analogs with higher affinity for certain sstr subreceptors, the next generation of somatostatin analogs, DOTA-TOC (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid Tyr$^3$ octreotide) was developed and labeled with different radionuclides for imaging as well as for therapy (de Jong et al. 1997; Otte et al. 1998, 1999; Paganelli et al. 2001; Pershagen 1998; Stolz et al. 1998; Waldherr et al. 2002). Replacement of the alcohol group at the C-terminus of the peptide by a carboxylic acid group results in the formation of DOTA-D-Phe1-Tyr$^3$-Thr$^8$-octreotide (DOTA-TATE), which has the highest affinity for the sstr2 receptor (Kwekkeboom et al. 2001; Reubi et al. 2000c, Antunes et al. 2007). However, the binding affinity to other sstr receptors has been less than expected; binding to sstr5 is low, to sstr3 is negligible, and there is no or very little affinity to sstr1 and sstr4 (Wild et al. 2003, Antunes et al. 2007). $^{111}$In-DOTA-lanreotide (LAN; D-2-Nal-Cys-tyr-D-Trp-Lys-Val-Thr-$NH_2$) was found to be superior to $^{111}$In-DTPA-octreotide for the detection of primary pancreatic adenocarcinomas (Raderer et al. 1998). However, the claim of Raderer et al. that 111In-DOTA-lanreotide targets sstr2–5 with higher affinity and sstr1 with lower affinity was not confirmed by Reubi et al. (2000c).

Next in the development were the third-generation somatostatin analogs such as DOTA-NOC (DOTA-1-Nal$^3$-octreotide), which was the result of an amino acid exchange at position 3 of octreotide. This compound has been shown to have improved affinity for sstr2 and higher affinity to sstr3 and sstr5 (Wild et al. 2003), resulting in coverage of a wider spectrum of sstr (pansomatostatin analog) and thereby improve the diagnosis of NET and various other somatostatin receptor-expressing tumors, for example malignant pheochromocytoma (Fig. 18.2), paraganglioma, and glomus tumors. After receptor binding, $^{68}$Ga-DOTA-NOC/DOTA-TOC is internalized

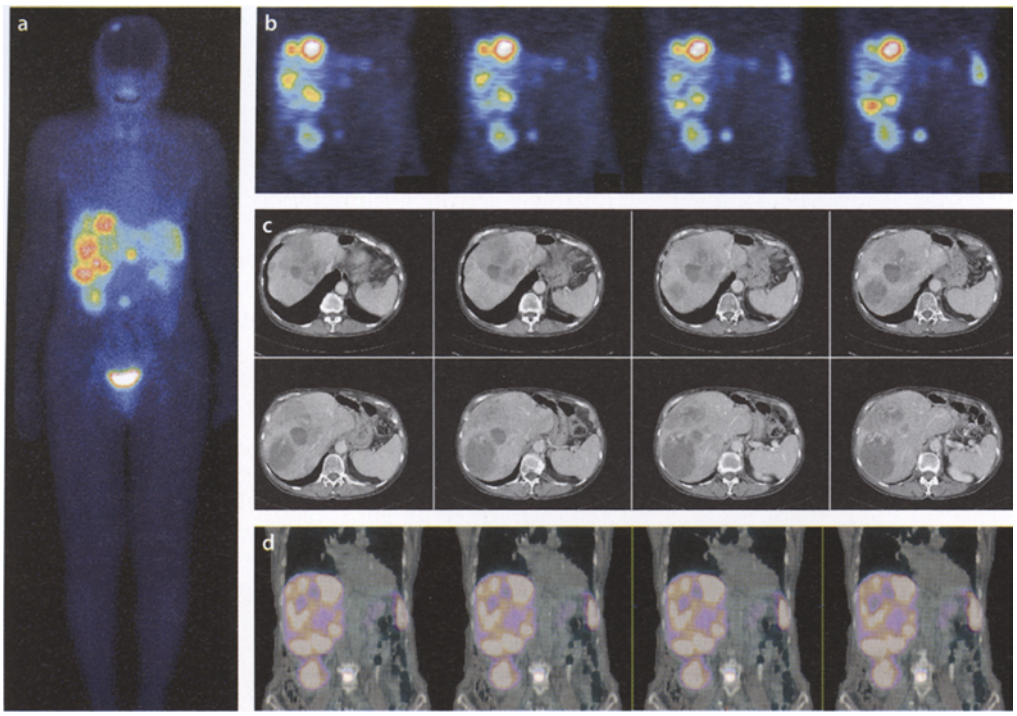


**Fig. 18.1a–d.** $^{99m}$Tc EDDA Hynic TOC whole-body scan: (**a** anterior view 1 h postinjection) and SPECT slices (**b** coronal view 2 h p.i.) demonstrating multiple liver metastases of a bronchus carcinoid operated 17 years before. In addition, bone metastases in the lumbar spine and in the skull are seen. **c** and **d** show the transaxial CT and coronal PET slices of the same patient using Ga-68 DOTA-NOC with intense accumulation of the somatostatin analog in the liver metastases

into the tumor cells with minimal washout of the peptides from the tumor cells thereafter (Henze et al. 2001, 2004, 2005). Other somatostatin analogs labeled with various radionuclides have been used for scintigraphy of sstr-positive tumors with variable success (Rufini et al. 2006). New somatostatin analogs that are in the preclinical stage of development are DOTA-NOC-ATE (DOTA-1Nal$^3$,Thr$^8$)-octreotide and DOTA-BOC and DOTA-BOC-ATE (DOTA, BzThi$^3$, Thr$^8$)-octreotide. Radiolabeled with 111In, they have been shown to have high affinity for sstr2, sstr3, and sstr5 and intermediate affinity to sstr4 (Ginj et al. 2005).

Also, SSTR antagonists such as (NH(2)-CO-c(DCys-Phe-Tyr-DAgl(8)(Me,2-naphthoyl)-Lys-Thr-Phe-Cys)-OH (sst(3)-ODN-8) and (sst(2)-ANT) have been labeled with $^{111}$In. Their superiority over SSTR agonists (in the mouse model) for in vivo targeting of SSTR2- and SSTR3-rich tumors, as shown by the group of Reubi (Ginj et al. 2006; Reubi et al. 2000b) has resulted in a paradigm shift and they are now being considered for tumor diagnosis.

#### 18.4.1.3 Radiolabeled Vasoactive Intestinal Peptide and Other Peptides for Diagnosis of NETs

VIP, a 28 amino acid peptide, initially isolated from porcine intestine, radiolabeled with either $^{99m}$Tc or I-123, has also been used for imaging NETs. Two subtypes of VIP receptors (VIPAC1 and VIPAC2) have been described. VIP receptors, predominantly VIPAC1, is expressed in the majority of common tumors: breast, prostate, lung, pancreas, colon, stomach, liver, and blad-

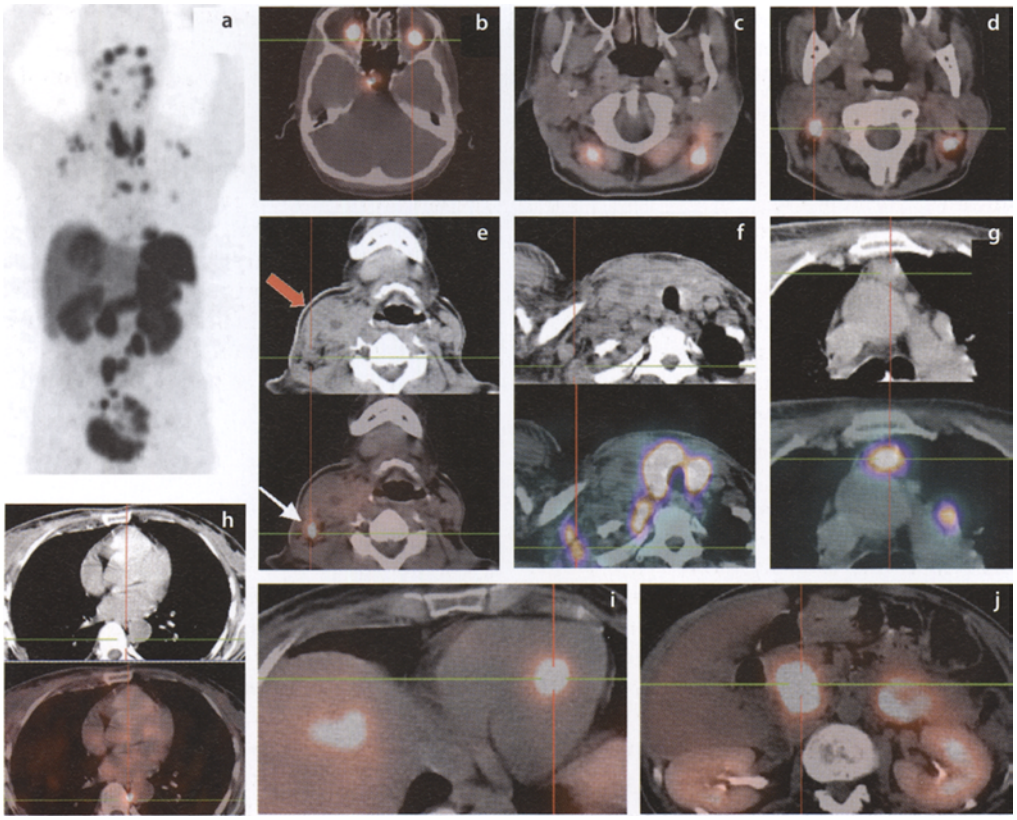


**Fig. 18.2a–j.** Heavily metastasizing, recurrent bilateral malignant pheochromocytoma: maximum intensity projection (MIP) image (**a**) and selected transversal Ga-68 DOTA-NOC PET/CT slices showing bilateral retrobulbar metastases (**b**) and subcutaneous (**c**) and cervical lymph node lesions (**d**). Specific uptake can be seen in a small lymph node metastasis in the right neck (**e**, *white arrow*), whereas a large parajugular abscess shows only blood pool activity (red arrow; see also CT scan). Further metastases are detected in the thyroid and in supraclavicular (**f**) as well as in mediastinal/para-aortic (**g**) lymph nodes and in a very small (Ø < 5 mm) prevertebral lesion (**h**). PET/CT also revealed a previously unknown myocardial metastasis (**i**) and strong uptake in multiple abdominal lesion (para-aortic lymph node metastases (**j**) and in a local recurrence)

der carcinomas. Leiomyomas predominantly express VPAC2 receptors, whereas paragangliomas, glial tumors, neuroblastomas, pituitary adenomas, pheochromocytomas, and endometrial carcinomas most commonly express VPAC1 receptors. Although only a few results have been published to date, their main indication is probably in the GEP neuroendocrine tumors (Moody et al. 2003; Reubi and Waser 2003; Thakur et al. 2000; Virgolini et al. 1994, 1995).

Other peptides that have been used for receptor scintigraphy of NET are cholecystokinin (CCK-B), gastrin, and bombesin (gastrin-releasing peptide) (Rufini et al. 2006). The experience with some of these radiolabeled peptides have been encouraging, but limited (Behe et al. 2003; Behr et al. 1998, 1999; Breeman et al. 1999; Kwekkeboom et al. 2000; Reubi et al. 1998).

#### 18.4.1.4 Other Radiopharmaceuticals Used in Nuclear Medicine for Imaging NETs

$^{99m}$Tc-sestamibi and $^{99m}$Tc-tetrofosmin have also been used for imaging melanomas and

small cell lung cancer but without much clinical success (Bombardieri et al. 2001; Takekawa et al. 1999). $^{99m}$Tc-DMSA was previously used frequently in medullary carcinoma thyroid (Ohta et al. 1984).

### 18.4.2 PET Radiopharmaceuticals

In spite of so many different radiopharmaceuticals used for the diagnosis, staging, and follow-up of NET patients with gamma camera-based scintigraphy, there has always been a compelling need to generate newer PET radiopharmaceuticals because of the superiority of PET imaging over gamma camera imaging. $^{18}$F-FDG $^{18}$F-fluoro-2-deoxy-d-glucose, 11C-5-HTP, $^{11}$C-5-hydroxy-l-tryptophan, $^{18}$F/$^{11}$C-DOPA, $^{18}$F-fluoro-phenylalanine, $^{68}$Ga-DOTA-TOC/$^{68}$Ga DOTA-NOC, $^{64}$Cu-TETA-octreotide (TETA= 1,4,8,11-tetraazacyclotetradecane-N′, N″, N‴, N⁗-tetraectic acid), and Gluc-Lys $^{18}$F-FP-TOCA (Nα-(1-deoxy-d-fructosyl)-Nε-(2-($^{18}$F)fluoropropionyl)-Lys$^0$-Tyr$^3$-octreotate, are some of the radiopharmaceuticals that have been used for imaging NET. The clinical results will be discussed separately. However, $^{68}$Ga needs special emphasis as it is heralded as a major breakthrough in the field of imaging for NET. $^{68}$Ga is readily available from a generator ($^{68}$Ge/$^{68}$Ga generator), making it less expensive and easier to handle as compared to other positron-emitting radionuclides (Maecke et al. 2005) such as $^{18}$F and $^{11}$C, which require an onsite cyclotron. $^{68}$Ge, the parent in the generator, is accelerator-produced (on $Ga^2O^3$ targets by a (p,2n) reaction) with a physical half-life of 270.8 days. $^{68}$Ga has a half-life of 68 min and decays mainly by positron emission (89%). The concept of using a $^{68}$Ge/$^{68}$Ga generator and a cold kit formulation was already proposed in 1993 (Deutsch 1993). Since then, several groups have been actively involved in the development of a better generator version and $^{68}$Ga-labeled peptides. Until now, several $^{68}$Ga peptides have been tested clinically for imaging somatostatin, melanocortin, and bombesin receptor-expressing tumors (Hofmann et al. 2001; Baum et al. 2007).

## 18.5 Radionuclide Imaging Methods

### 18.5.1 Single Photon Emission Computed Tomography vs Planar Imaging

The major disadvantage of planar imaging is the lack of precise localization of the tumor site as it is two-dimensional. Single photon emission computed tomography (SPECT) has the advantage of 3D reconstruction and thus assists in better localization. Several studies have shown that SPECT is more sensitive to planar imaging for detection of deep-seated tumors.

### 18.5.2 SPECT vs PET

One disadvantage of SPECT imaging is that quantification is very difficult and not routinely performed in practice. Objective methods for follow-up of cancer patients under strict guidelines (such as EORTC, RECIST, WHO) are essential for better patient management. In our experience, this is best carried out using PET/CT. The higher resolution of PET images is also a significant advantage compared to SPECT. The only limiting factor with PET is the higher cost of the equipment, making SPECT the most commonly used imaging method in oncology in various countries (especially in less developed or developing countries). The maintenance of cyclotron units and the implementation of good manufacturing practices has made the running cost of a fully functional PET–cyclotron unit very high and beyond the reach of many developing countries. This is where the in-house positron emitting radionuclide generators, because of their low cost and easy availability, will play an important role in the future.

### 18.5.3 SPECT Versus SPECT/CT and PET vs PET/CT

Nuclear medicine imaging in general lacks sufficient anatomical details. The addition of CT to SPECT or PET data helps in the precise localization of tumors. In addition, the present generation of gamma cameras/PET scanners have

an embedded CT in the gantry, which makes it possible to perform contrast-enhanced CT with high resolution. In one sitting, it is possible to obtain both anatomical information and functional information. Indeed, PET/CT is already being heralded as the next-generation imaging methodology.

## 18.6 Clinical Indications for PET or PET/CT in NETs

Based upon our own PET/CT experience and the review of the literature, the following indications are important:

- Diagnosis and staging of NET.
- Defining the prognosis of patients (under investigation).
- Follow-up of patients after surgery.
- Follow-up of patients after somatostatin analog therapy.
- Choosing the appropriate therapeutic regime for PRRT (under investigation).
- Predicting the response after PRRT.
- PET/CT can be used for choosing the best therapy monitoring protocol for NET (molecular vs anatomical imaging).

## 18.7 Clinical Studies

### 18.7.1 $^{18}$F-FDG PET

$^{18}$F-FDG PET is increasingly being used for various oncological indications. $^{18}$F-FDG is useful for evaluating tumor hexokinase activity, which is increased in tumor cells because of the accelerated rate of glycolysis. $^{18}$F-FDG PET is primarily used in tumors for the purpose of diagnosis, staging, restaging, and evaluation of the response to treatment. The main use of FDG-PET in diagnosis of NETs depends on the grade of differentiation and/or aggressiveness of NETs (Adams et al. 1998; Eriksson et al. 2000; Pasquali et al. 1998; Scanga et al. 2004; Sundin et al. 2004; Zhao et al. 2002).

A study comparing 111In-pentetreotide somatostatin receptor scintigraphy (SS-R),$^{18}$F-FDG PET, and $^{99m}$Tc(V)DMSA scintigraphy (dual radionuclide technique, DNS = SS-R+ $^{99m}$Tc(V)DMSA) in patients with GEP and medullary thyroid carcinoma (Adams et al. 1998) has shown that FDG-PET is more sensitive than SS-R in picking up less differentiated GEP tumors (Figs. 18.3–18.5) but is less sensitive than SS-R in the detection of differentiated GEP tumors. In patients with recurrent MTC and rapidly increasing CEA levels, FDG-PET was found to be superior to DNS. Based on these observations, the authors of the study concluded that $^{18}$F-FDG PET should be performed only if SS-R or DNS studies were negative. In another study conducted on 16 patients with NET (Pasquali et al. 1998), FDG uptake in NETs was related to the aggressiveness and rapid growth of the tumor and denoted worse prognosis. It was also concluded in the study that FDG-PET contributes to better staging of the advanced diseases as compared to CT scan and SS-R. In a multicenter study, FDG-PET was found to be a useful method for the staging and follow-up of patients, as it has the highest lesion detection probability for MTC tissues as compared to other imaging modalities such as $^{99m}$Tc(V) DMSA, SS-R,CT, etc. (Diehl et al. 2001). In NET of the pancreatic-duodenal region, FDG PET was found to have the potential to change the treatment protocol in 17% of patients. FDG-PET was proved to be the second-line technique in pancreatic-duodenal region NETs. The authors of the study found that FDG-PET was best suited for patients suspected of having malignant tumor or having a pancreatic mass greater than 2 cm or MEN I cases with at least one visible lesion. FDG-PET was found not to be useful in duodenal tumors, benign insulinomas, and small single pancreatic neuroendocrine lesions (Pasquali et al. 2004).

However, in spite of these successful results, one major limitation of FDG as a tumor marker is that it is not completely specific for tumors. FDG is known to accumulate in inflammatory lesions also, thereby increasing the false-positivity rate.

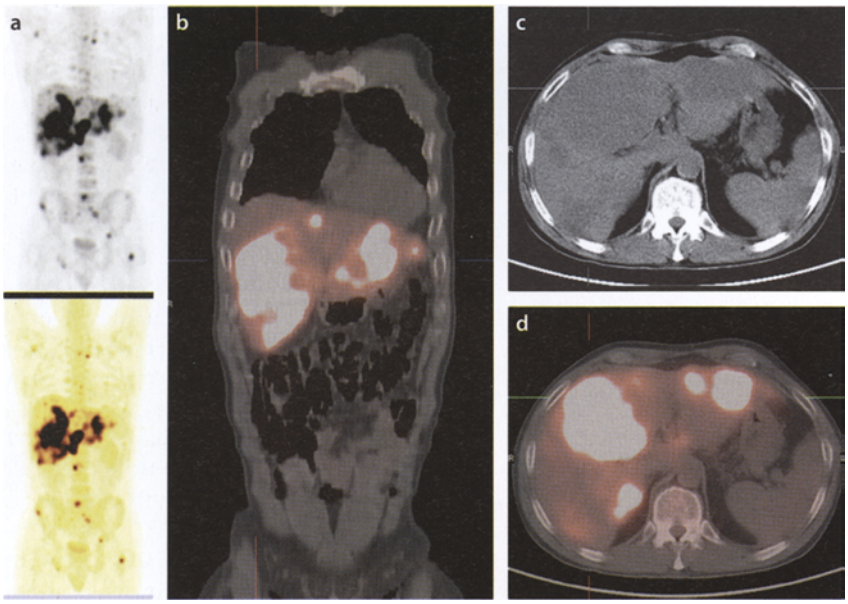


**Fig. 18.3a–d.** F-18 FDG PET/CT in a 43-year-old patient with neuroendocrine pancreatic cancer (proliferation rate <10%, synaptophysin and chromogranin A staining positive) diagnosed 4 months earlier. MIP image (**a**), coronal PET/CT fusion image (**b**), CT (**c**), and transversal PET/CT fusion image (**d**) demonstrate multiple FDG-avid metastases before therapy

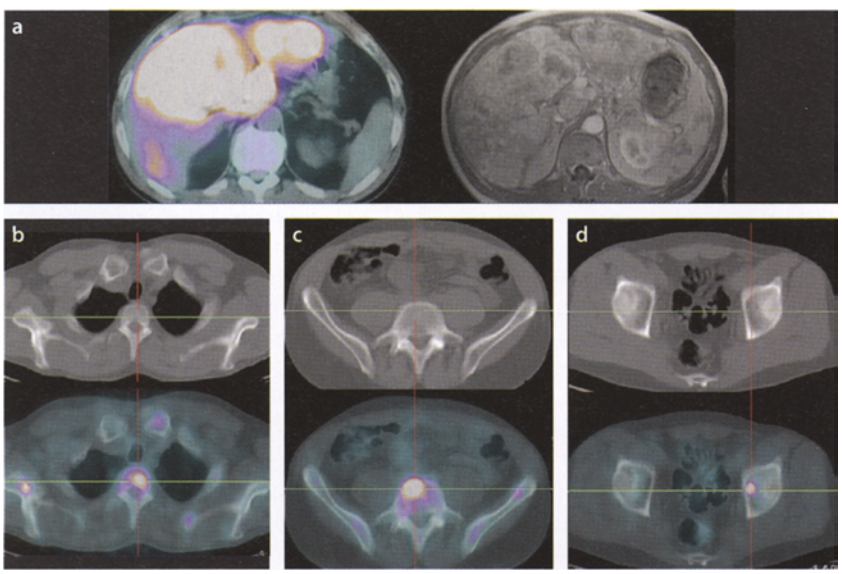


**Fig. 18.4a–d.** Same patient as described in Figure 18.3. Extensive, bilobar liver metastases (**a**) as shown by F-18 FDG-PET/CT (upper left row, highest glucose metabolism in segment VII with an standard uptake value (SUV) of 29.1) and MRI (upper right image). Hypermetabolic bone metastases are detected by FDG-PET in the thoracic spine and in the right scapula (**b**), in the lumbar spine in L5 (**c**), and in the left acetabulum (**d**), whereas the CT scan is still normal (i.e., the lesions are located mainly in the bone marrow)

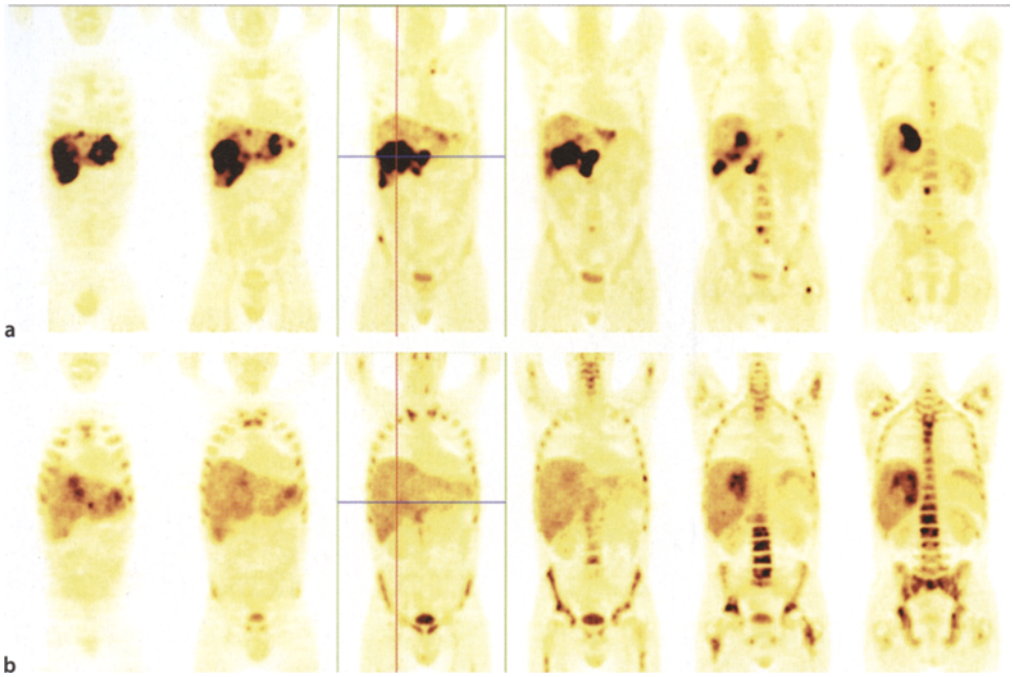


**Fig. 18.5a,b.** Same patient as described in Figure 18.3. F-18 FDG PET/CT (coronal slices) before (**a**) and after (**b**) combined peptide receptor radiotherapy (PRRT, 2 cycles of Y-90 DOTA-TATE, total administered activity 7.5 GBq) and chemotherapy (TCE scheme, Taxol, carboplatin, etoposide) with impressive metabolic response after combined treatment. Note activation of normal bone marrow in the spine after G-CSF therapy (upper right panel **b**)

### 18.7.2 $^{18}$F-DOPA PET

NETs are known to accumulate and decarboxylate 5'-hydroxytryptamine and l-3,4-dihydroxyphenylalanine (l-DOPA) (Pearse 1969). An increase in the activity of l-DOPA decarboxylase is one of the hallmarks of NETs (Baylin et al. 1980; Berger et al. 1984; Gazdar et al. 1988). The first study that demonstrated the utility of 11C-DOPA in the detection of pancreatic tumor was conducted by Ahlstrom et al. (1995). $^{18}$F-FDOPA PET has also been found to be useful in advanced NET. One study found that $^{18}$F-FDOPA performs better than SS-R scintigraphy in visualizing NETs. The authors also proposed that $^{18}$F-FDOPA performs better than CT in detection of bone lesions (Becherer et al. 2004). However, in small cell lung cancer, $^{18}$F-FDOPA was found to be of no use, whereas $^{18}$F FDG PET had a significant role (Jacob et al. 2003). In patients with pheochromocytoma, both $^{18}$F-FDOPA PET and MRI were found to be superior to $^{131}$I MIBG study with sensitivity and specificity of 100% (Hoegerle et al. 2002). However, this study cannot be taken as a reference study because the imaging method ($^{131}$I MIBG scintigraphy) with which the PET study and MRI study was compared is not the current gold standard (SS-R) for the detection of NETs.

The potential limitation of $^{18}$FDOPA-PET is the normally high uptake in the duodenum and pancreas (Fig. 18.6), which might cause problems in localization of tumors in these regions. Apart from this, the nonspecific accumulation of $^{18}$FDOPA in the intestine is a potential source of false-positive interpretations.

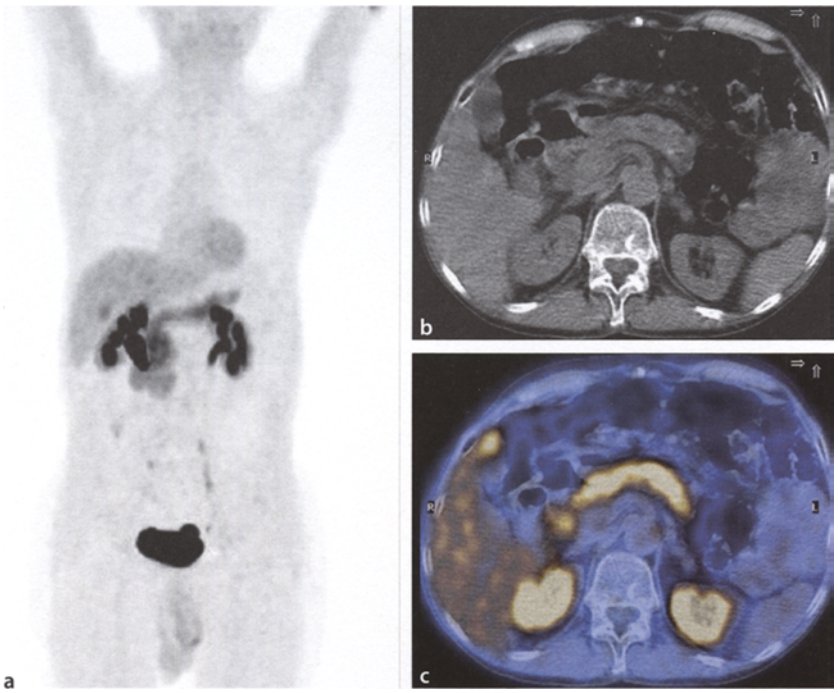


**Fig. 18.6a–c.** F-18 DOPA PET/CT showing physiological high uptake in the pancreas: MIP image (**a**), CT scan (**b**), and PET/CT fusion image (**c**). (Image courtesy of Stefano Fanti, University of Bologna)

### 18.7.3 $^{11}$C-5-HTP

In a study comparing 5-HTP-PET with CT and somatostatin receptor scintigraphy in patients with carcinoid and endocrine pancreatic tumors, 5-HTP-PET was found to be superior to CT and somatostatin receptor scintigraphy for tumor visualization. Many small, previously overlooked lesions were diagnosed by $^{11}$C-5-HTP-PET (Eriksson et al. 2000; Orlefors et al. 1998).

### 18.7.4 $^{68}$Ga-DOTANOC/DOTATOC Receptor PET/CT

Somatostatin receptor scintigraphy has been validated as the most specific tool for the detection of NETs and is used extensively for the follow-up of patients after receiving somatostatin analog therapy. However, some of the studies that have compared nonsomatostatin PET radiopharmaceuticals and SS-R have found that, in some cases, the PET study was more sensitive in picking up tumor lesions. This may be attributed to the decreased sensitivity of gamma camera imaging methods as compared to PET. This fact plus the need to evaluate the effect of rapidly progressive role of peptide receptor therapy based on somatostatin analog made scientists work toward finding a positron emitting radionuclide that could be tagged with somatostatin analogs. The ability to tag somatostatin analogs with $^{68}$Ga has revolutionized the role of PET in diagnosis, staging, and therapy monitoring of patients with receptor-positive NETs. One of the advantages of the $^{68}$Ga-DOTANOC/DOTATOC PET or PET/CT study over $^{111}$In-octreotide scintigraphy is better visualization of deep-seated lesions, which are difficult to be seen on planar and SPECT images (Kwekkeboom

et al. 1994). The normal physiologic distribution along with the SUVmax value has been calculated by these authors (Baum and Prasad 2006). This information is essential for proper interpretation of images as well as for defining a cut-off value for malignant lesions. In a preliminary clinical study, Hofmann et al. (2001) showed that $^{68}$Ga-DOTATOC is superior to $^{111}$In-octreotide SPECT (CT was taken as the reference for comparison) in detecting upper abdominal metastases. Kowalski et al. (2003) also showed that in comparison to the [$^{111}$In]-DTPAOC-scan, $^{68}$Ga-DOTATOC PET appears to be superior, especially in detecting small tumors or tumors bearing only a low density of somatostatin receptors (SSTRs). Apart from this, $^{68}$Ga-DOTATOC PET has also been envisaged to have a potential role in the small cell lung cancer, as it is known to express somatostatin receptor and thus is a potential candidate for PRRT with $^{90}$Y-DOTATOC/DOTATATE (Maecke et al. 2005). In unpublished data in more than 800 $^{68}$Ga-DOTANOC PET/CT studies conducted by the authors of this article to date, it was found that:

- $^{68}$Ga-DOTANOC PET was able to pick up many lesions which could not be picked up by CT (Fig. 18.7).
- $^{68}$Ga-DOTANOC PET is of significant value in therapy monitoring (Figs. 18.8, 18.9) of patients with NET (total number of patients treated, n=358) having received PRRT.
- PET/CT provides additional information about the tumor as compared to PET study alone.
- $^{68}$Ga-DOTA-NOC PET/CT is a useful adjunct in deciding the amount of radioactivity to be administered for PRRT.

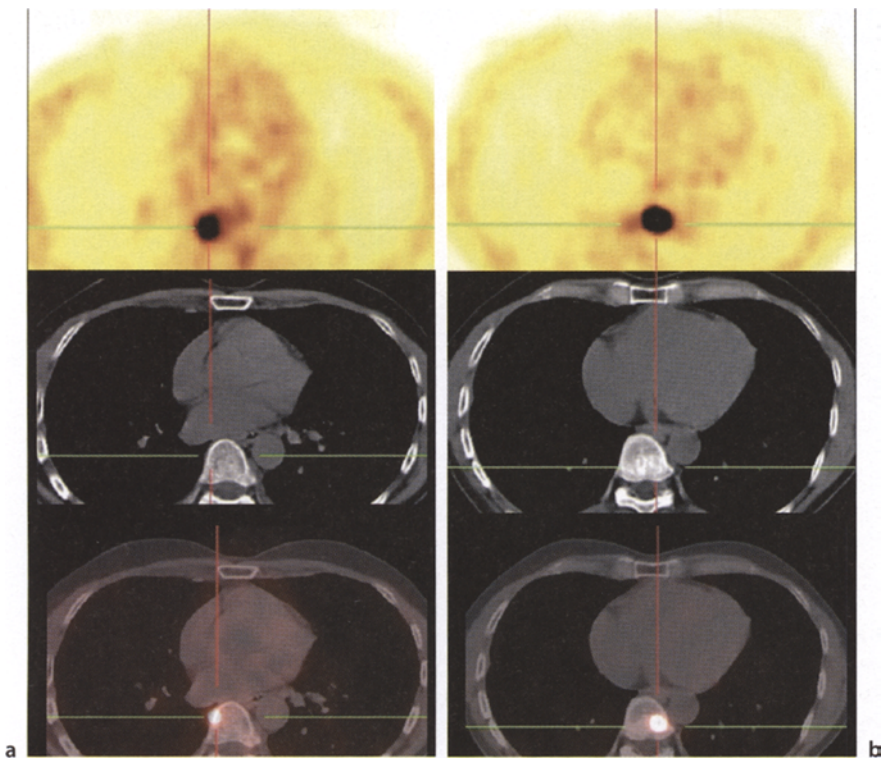


**Fig. 18.7a,b.** Vertebral bone metastases of ileum carcinoid. Osteoblastic, receptor-positive lesion on CT in one thoracic vertebra (**a**), whereas another lesion, with strong, focal SMS-receptor expression on Ga-68 DOTA-NOC-PET, is invisible on CT scan (**b**)

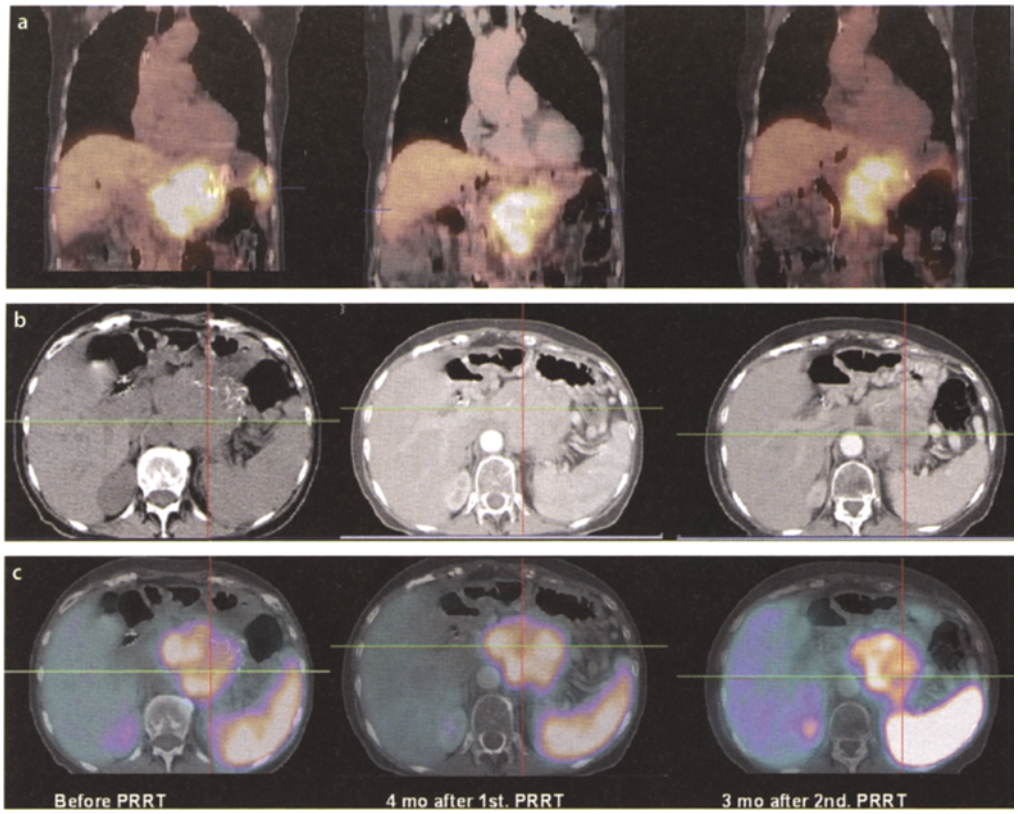


**Fig. 18.8a–c.** Large, inoperable neuroendocrine carcinoma of the pancreatic tail with infiltration of the stomach. Ga-68 DOTA-NOC receptor PET/CT (**a** coronal PET slices, **b** transversal CT slices, and **c** fused images before intra-arterial PRRT using Y-90 DOTA-TATE, 4 months after the first treatment, and 3 months after the second intra-arterial therapy) showing high but heterogeneous SMS-receptor expression. Before treatment, the 66-year-old patient needed multiple blood transfusions despite intense conventional treatment, including chemotherapy and Sandostatin. After the second PRRT, the bleeding stopped completely

In an intraindividual study comparing the diagnostic efficacy of $^{68}$Ga DOTA-NOC and $^{68}$Ga DOTA–TATE, our group (Antunes et al. 2007) demonstrated for the first time that $^{68}$Ga DOTA-NOC is superior to $^{68}$Ga DOTA–TATE. Koukouraki et al. (2006) found that based on the pharmacokinetic data of $^{68}$Ga-DOTA-TOC, it is possible to separate the blood background activity from the receptor binding, which is potentially a very significant observation as it may help in optimizing the planning of $^{90}$Y-DOTA-TOC therapy.

In summary, among several advantages of $^{68}$Ga-somatostatin analogs over other nonsomatostatin analog-based PET radiopharmaceuticals for the detection and staging of NETs, the most important ones are kit formulation, easy availability, higher specificity, and the ability to monitor therapy and follow-up of NET patients.

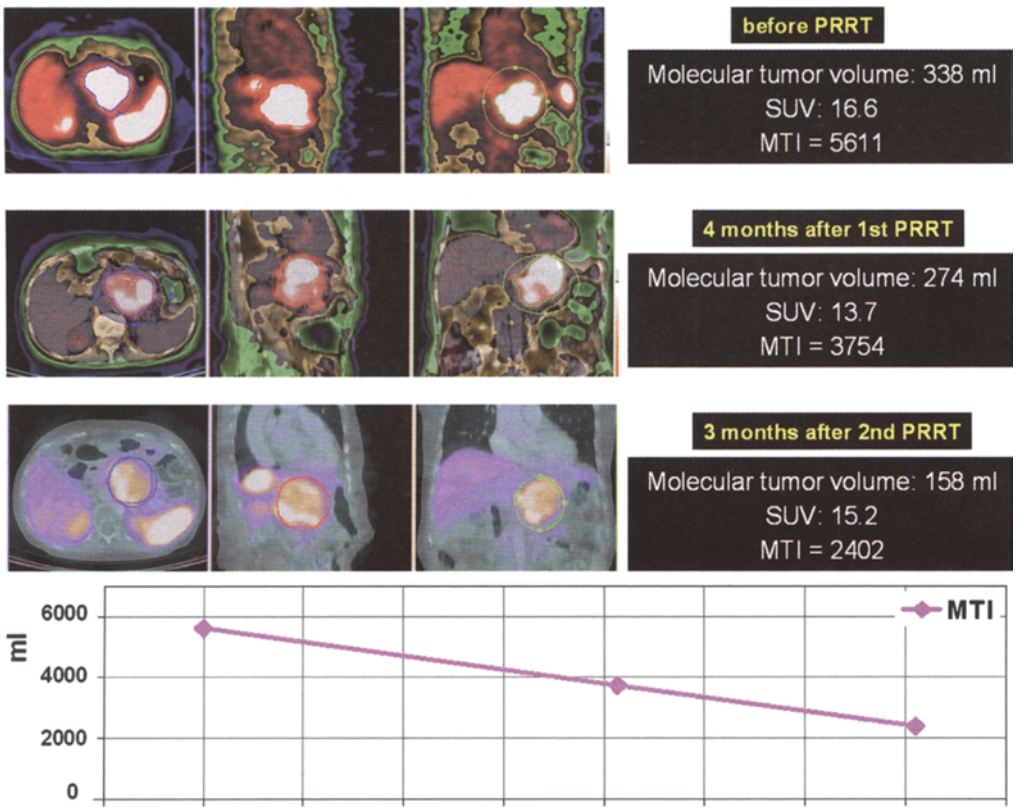


**Fig. 18.9.** Molecular imaging for measuring response after therapy by calculating the molecular tumor index using ROI technique and Ga-68 DOTA-NOC receptor PET/CT. Metabolic/molecular tumor index (MTI) = molecular tumor volume (MTV) multiplied by SUV. The significant decrease in MTI over time correlated with the improvement of the patient's clinical symptoms

### 18.7.5 Gluc-Lys (($^{18}$F)FP)-TOCA PET

The success of $^{68}$G-DOTA-TOC/DOTA-NOC has encouraged the use of $^{18}$F as the radioligand for somatostatin analogs. Gluc-Lys (($^{18}$F)FP)-TOCA is a recently developed $^{18}$F-labeled somatostatin analog. A preliminary comparative study found that Gluc-Lys (($^{18}$F)FP)-TOCA PET is superior to a 111In-DTPA-octreotide scan in the diagnosis of NETs. In the same study (based on a literature survey), it was stressed that Gluc-Lys (($^{18}$F)FP)-TOCA PET is comparable with $^{68}$Ga-DOTA-TOC/DOTA-NOC PET findings in NETs (Meisetschlager et al. 2006).

### 18.7.6 $^{64}$Cu-TETA-Octreotide PET

$^{64}$Cu (half-life, 12.7 h; β+ 0.653 MeV [17.4%]; β−, 0.579 MeV [39%], 43.6% electron capture) is being investigated and has shown good potential as a positron emitting radionuclide for PET imaging and radiotherapy (Anderson et al. 2001; Lewis et al. 1999; Wang et al. 2003). The possibility of performing dosimetry for PRRT based on $^{64}$Cu is another big advantage. In a preliminary study $^{64}$Cu-TETA-octreotide PET has been found to have high sensitivity as well as favorable dosimetry and pharmacokinetics (Anderson et al. 2001).

## 18.8 Conclusion and Future Directions

Somatostatin receptor scintigraphy has revolutionized the diagnosis of NET. The rapidly growing number of new radiopharmaceuticals and the greater understanding of the molecular basis of NETs has helped tremendously in the management of patients with neuroendocrine tumors. Future studies with receptor PET/CT need to be directed toward optimizing the therapeutic dose for PRRT of NETs. The possibility of performing both therapy and imaging with the same radiopharmaceutical (e.g., using $^{64}$Cu-TETA-octreotide) could be an advantage over the currently used PET radiopharmaceuticals. Novel somatostatin analogs need to be rigorously tested for high affinity toward sstr subtypes and may enable even better treatment of NETs then what is possible today.

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