Efficient Diagnosis of Neuroendocrine Tumors of the Gastro-entero-pancreatic System

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Diagnosis as a process of decision making ranging beginning with the symptoms through to the development of a disease and as a process of gaining knowledge about the nature and spreading of a disease is of significant importance for patients with neuroendocrine tumors. Diagnosis takes place through anamnesis, clinical and laboratory tests, and imaging procedures whose value will be presented briefly in the following. The diagnostic tests discussed here must be interpreted and evaluated in terms of sensitivity, specificity, necessity, availability, expertise and cost.

For patients with neuroendocrine tumors the following are the main questions to be answered at the beginning and repeatedly during the course of the disease:

- Where is the primary tumor located and is it resectable?
- Are metastases present and are these resectable?
- How is tumor biology to be classified and is a functional syndrome present?
- Does a risk of second tumors exist and is there a family history of the disease?

Neuroendocrine tumors (NETs) can be accompanied by functional syndromes which are distinguished by typical clinical symptoms. In ideal cases, the diagnosis can already be made at the time of anamnesis, e.g. an insulinoma in the presence of neuroglucopenia triggered by fasting or physical labor, a VIPoma in the case of secretory diarrhea, or a carcinoid syndrome in the case of flush and diarrhea. Most NETs are, however, functionally inactive, although they form and secrete hormones and peptides, e.g. chromogranin A, neuron-specific enolase (NSE), or pancreatic polypeptide (PP), which nevertheless do not lead to any symptoms. These proteins can, however, be used as tumor markers for determination in serum. Functionally inactive NETs usually become clinically noticeable through local growth accompanied by complaints or through a desmoplastic reaction of the mesenterium ("bowel ischemia"). Often these complaints are misinterpreted for years as a functional bowel syndrome. Since NETs of the midgut with heavily increased serotonin production can cause heart disease (carcinoid heart disease), the tumor is often only diagnosed upon clarification of heart failure (detection by chance of hepatic metastases during echocardiography).

NETs can also occur in the context of germline mutations (multiple endocrine neoplasia (MEN) types I, II A, II B, III, along with von Hippel Lindau syndrome and neurofibromatosis; see article on classification and pathogenesis of NETs). For this reason, precise documentation of family case history is important. Germline mutations can also come into existence *de novo* and, as a result, must be taken into consideration repeatedly to eventually include progeny of the patients early on in monitoring programs, especially regarding MEN type II, where – depending upon mutation in the RET oncogene – an early, prophylactic thyroidectomy is recommended.

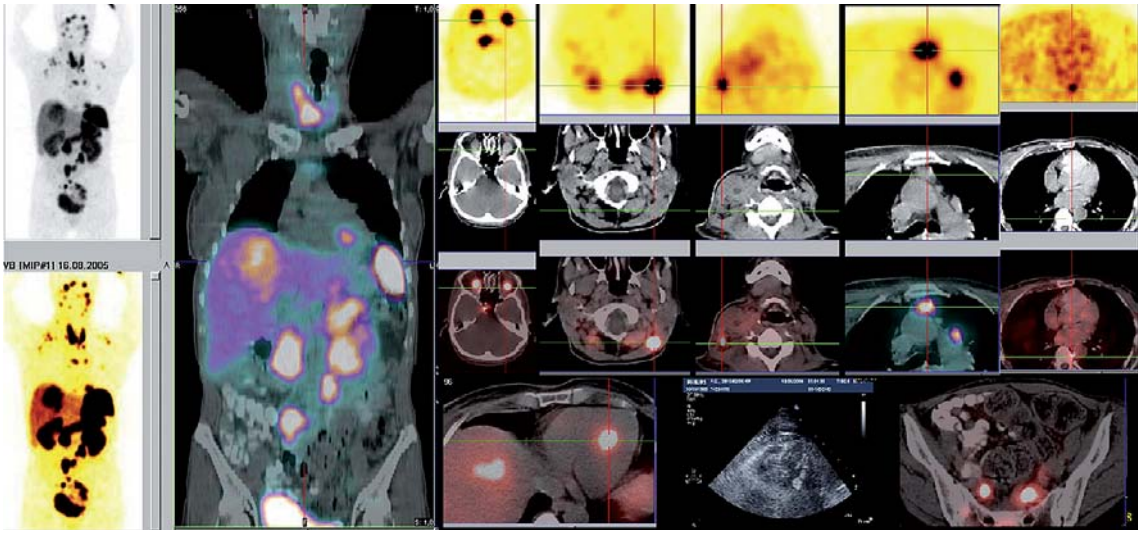

Figure 1

Full-body receptor PET/CT with ^{68}Ga-DOTA-NOC. Left: screening image (MIP) with detection of a disseminated metastasis (paraganglioma/pheochromocytoma syndrome), right: transversal PET/CT single slice images. Metastases are imaged at the following localizations (from upper left to lower right)): retro-orbital on both sides (clinical exophthalmus), in the galea, parajugular in one lymph node (a simultaneously existing abscess in the neck area shows no increased tracer uptake), mediastinal/para-aortal and paraoesophageal lymph nodes, intracardial (confirmation on echocardiogram) and abdominal presacral. Altogether, over 60 metastatic localizations were detectable. Following three radioreceptor therapy treatments, the patient went into a partial remission lasting over two years.

During clinical examination, attention is to be paid to signs of endocrinopathies, for instance, adipositas in insuloma patients, necrolytic migratory exanthema in cases of glucagonoma, or flushing triggered by liver palpation in cases of carcinoid syndrome. The non-endocrine active, non-functional NETs usually make themselves clinically noticeable through indirect signs of advanced tumor disease, such as weight loss, jaundice, ileus, or symptoms of intestinal stenosis. Along with documentation of the possible presence of an enlarged liver or spleen, thorough auscultation of the abdomen is urgent concerning NETs of the midgut in order to detect symptoms of intestinal stenosis caused by the desmoplastic reaction of these tumors. Cardiac disease with endocardial fibrosis (so-called Hedinger syndrome) brought on by a carcinoid makes itself clinically perceivable through increasing right-ventricular failure (tricuspid regurgitation). Thorough echocardiographic examination is therefore necessary to avoid missing the point in time for surgical intervention.

During the course of disease, many patients suffer substantial weight loss that can extend to cachexia which is associated with a poor prognosis and limited therapeutic options. As a result, along with determining patient size and weight, their weight should also be tracked and signs of malnutrition watched for.

Primarily the determination of chromogranin A (CgA), a component of the secretory vesicle of endocrine-active cells, has proven itself as a tumor marker. In the case of functionally active NETs, the hormone or messenger substance secreted in excess should be determined during the course of disease, for example, gastrin in the case of Zollinger Ellison syndrome or the serotonin metabolic product 5-hydroxy indole acetic acid in urine or serotonin in serum when carcinoid syndrome is concerned. The pancreatic polypeptide (PP) is also considered a well-suited tumor marker, but is determined less often than CgA as a progression parameter. The elevated level of the tumor marker does not always correlate closely with the tumor mass; however, a rapid increase of CgA is considered an unfavorable prognostic sign for the disease's progression. In principle, tumor markers should first be determined after the diagnosis of NET has been confirmed and not for the purpose of screening in suspected cases to avoid an expensive and unnecessary excess of diagnostic testing. Elevated levels of CgA

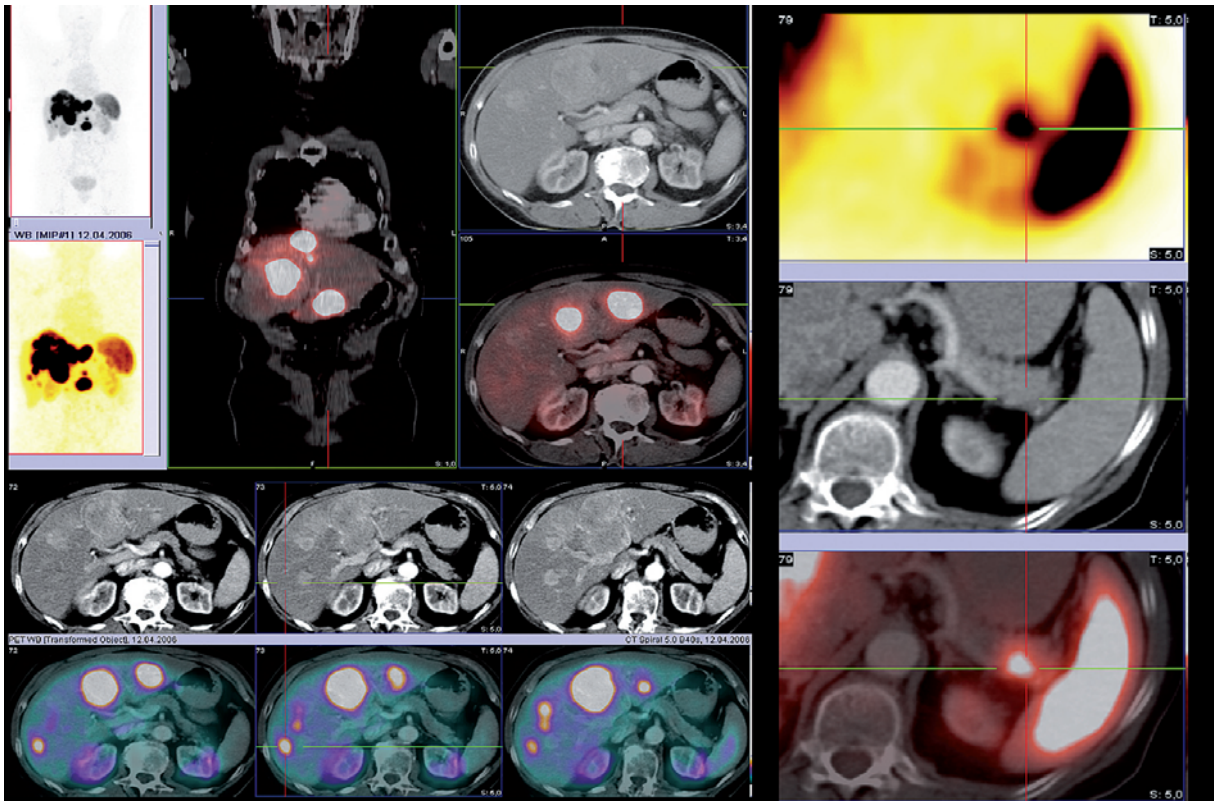

Figure 2

CUP syndrome (bioptic detection of metastases of an NET in the liver). Detection of the primary tumor in the pancreatic cauda during ^{68}Ga-DOTA-NOC receptor PET/CT (image at lower right, in the CT there is not yet any clear pathological changes) and expanded receptor-positive liver metastases.

can also occur in cases of chronic atrophic gastritis, kidney failure, or unspecific ailments.

In terms of imaging diagnostics, ultrasound, scintigraphy, CT, MRT, and endoscopic examinations have proven themselves as the standard diagnostic procedures. As further developments of these techniques, contrast-enhanced ultrasound, endosonography, and above all positron emission tomography in combination with x-ray computed tomography (PET/CT) can substantially improve the sensitivity and specificity of the diagnosis. In general, a functional imaging procedure for the purpose of full-body diagnostic testing and an imaging procedure with the highest resolution and most specific imaging possible are recommended, as in the guidelines also.

Screening is based on radiological detection of the NETs through the binding or uptake of labeled radiopharmaceuticals by the tumor cells. Tumor scintigraphy with ^{123}iodine-meta-iodobenzylguanidine (MIBG) is the longest used nuclear test (in Europe). MIBG is absorbed into the cells through vesicular monoamine transporters. Substantially more sensitive for detecting somatostatin receptors on the NETs are labeled peptides. Belonging to these are somatostatin analogs, such as octreotide acetate or other somatostatin receptor analogs which are labeled with ^{111}Indium (OctreoScan) or ^{99m}Technetium. ^{111}Indium octreotide (OctreoScan) is presently still considered to be the gold standard among radiological diagnostics for NETs. Significantly more sensitive – detection of 40 - 60% more tumor lesions – and more specific are, however, ^{68}Gallium-labeled receptor ligands, such as ^{68}Gallium-DOTA-TOC, ^{68}Gallium-DOTA-NOC, and ^{68}Gallium-DOTA-TATE which are used in positron emission tomography combined

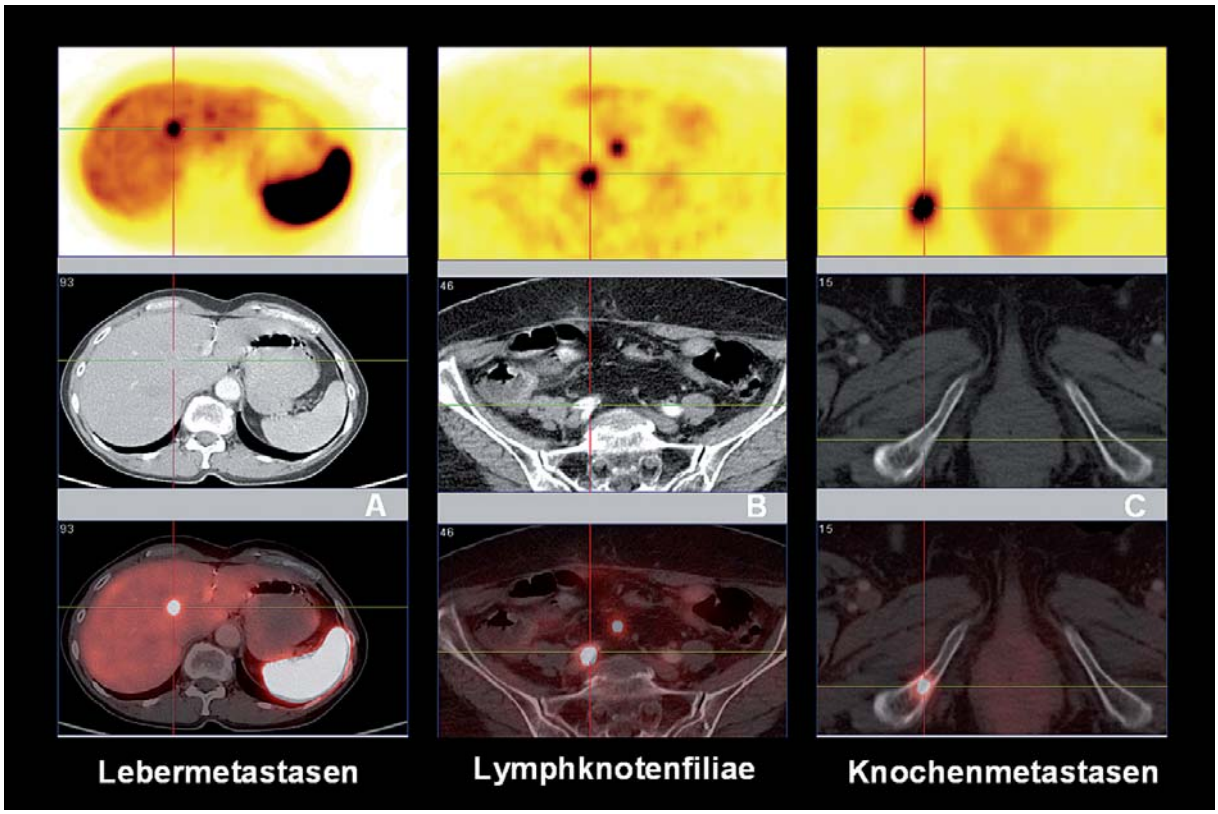

Figure 3
^{68}Ga-DOTA-NOC receptor PET/CT: Detection of somatostatin receptor-positive liver, lymph node, and bone metastases.

with x-ray computed tomography (receptor PET/CT). With receptor PET/CT based on ^{68}Gallium-labeled peptides, virtually all well-differentiated NETs (WHO 1-2) and other neuroendocrine tumors with high somatostatin receptor density up to a size of a few millimeters can be imaged and precisely localized (Figure 1). The poorly-differentiated NETs (WHO 3), which distinguish themselves through a high rate of proliferation and an increased glucose metabolism, can be better detected using ^{18}F-2-deoxy-2-Fluor-D-glucose (FDG) PET/CT. In contrast, there is frequently no increased glucose metabolism determinable with well-differentiated NETs. The combination of the PET procedure with x-ray computed tomography ("anato-molecular imaging") allows for exact anatomical localization of the NET foci at the same time. If PET/CT is not available, then the affected regions should be imaged (e.g. with MRT or CT) after the screening process (octreotide scintigraphy plus SPECT). Ideally, this would be followed by a SPECT-CT image fusion using software.

The sensitivity and specificity of radiological imaging diagnostics depend to a great extent on technical factors, such as equipment type and use of contrast media. Generally, computed tomography is recommended as the basic test and nuclear resonance imaging more for problematic cases. In the guidelines the two procedures are considered to be of equal value. Nuclear resonance imaging is primarily used in the detection of brain metastases, in cases of small liver metastases, before liver resections, as well as in cases of masses in the pelvis minor and for detecting bone metastases. The same fundamentals as for other tumors apply to radiological detection of NETs so that the choice of method should depend on sensitivity, specificity, availability, experience, and radiation exposure. The most elegant and quickest solution for staging patients with NETs is

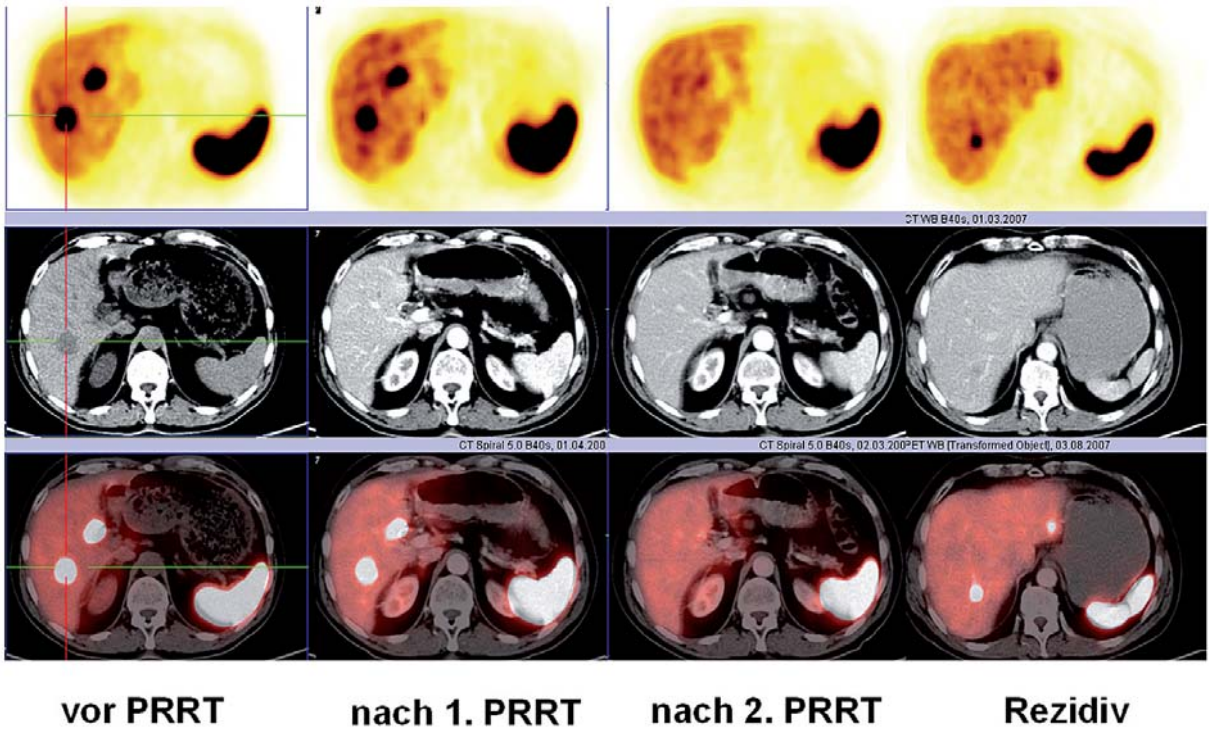

Figure 4

Tracking of progression following radioreceptor therapy using ^{68}Ga-DOTA-NOC PET/CT: complete remission after the second round not only according to PET molecular imaging criteria, but also morphologically in CT. Recidivation of liver metastases at a different localization after over 12 months.

offered by combining a highly sensitive procedure (^{68}Ga DOTA-SMS Receptor PET) with an integrated CT (PET/CT) for the most precise anatomical localization (Figure 2). Receptor PET/CT is also of particular importance in tracking the progression of therapy since along with the size of the lesions, receptor density can also be evaluated which, in turn, is of great importance in deciding which further, differentiated therapy should follow (Figure 3).

Transabdominal ultrasound is the imaging procedure most often used. Although the sensitivity is limited with 50-80%, it can, however, be increased with special image processing, such as *tissue harmonic imaging,* or through the use of a contrast medium which clearly increases the sensitivity and specificity primarily in the detection of hepatic metastases. However, metastases of NETs in the liver do not regularly show hypoechogenicity in the portal venous contrast medium phase, in contrast to metastases of other tumors. As a dynamic examination, ultrasound has the undisputed advantage that in the interaction with the patient, painful areas can be examined specifically and in addition functional statements can be made, for instance, on circulation or action of the bowels. Ultrasound also makes specific and controlled biopsy or puncture possible during the same session. As a result, transabdominal ultrasound is the "work horse" in terms of staging patients. Endoscopic ultrasound (EUS) allows for the most precise analysis of all organs neighboring the upper or lower gastrointestinal tract. Particularly for evaluation of the pancreas, bile ducts, or wall of the duodenum or stomach, as well as in cases of rectal tumors, EUS is an indispensible imaging tool; likewise for monitoring small NETs of the pancreas in cases of MEN1 through its excellent resolution in the millimeter range. However, just as with transcutaneous ultrasound, the procedure is very dependent on the

examiner. In addition, endoscopic ultrasound allows for a biopsy to be taken through targeted puncture with a 19-G needle for cytological, or ideally for histological, analysis. Therapeutic interventions are also increasingly performed through endoscopic ultrasound, such as draining abscesses or infected pseudo-cysts or draining off bile or pancreatic secretion if ERCP is not possible. Therapeutic endosonography can also be used to treat pain (plexus coeliacus block).

Endoscopic examinations are necessary in the search for a primary tumor in the gastrointestinal tract. Rectal NETs are frequently removed as being a polypous mass in the context of a check-up coloscopy and often first recognized for being what they are after histological analysis. NETs in the terminal ileum cannot always be recognized retrograde over the Bauhin's valve during a coloscopy; in this case, localization of the primary tumor can possibly be reliably done through capsule endoscopy or double-balloon enteroscopy. An important role is also played by endoscopy in the diagnosis of NETs of the stomach, which in the case of type 1 NETs can often be removed endoscopically at the same time through polypectomy or mucosectomy.

Literature available from the authors upon request

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