⚕ Thieme

Update Regarding Imaging of Neuroendocrine Neoplasms
Update Bildgebung neuroendokrine Neoplasien

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ABSTRACT

Background Neuroendocrine neoplasms (NEN) are a heterogeneous group of tumors characterized by the expression of typical proteins. A wide range of morphological and functional imaging methods is required in order to adequately assess the course of the disease and to optimally treat the patient. The spectrum of indications ranges from the detection of small primary tumors to the documentation of the metastasis pattern and the assessment of the suitability for certain invasive or noninvasive therapy methods. The exact recording and quantification of findings is indispensable.

Methods This article is based on a comprehensive literature search on the different aspects of neuroendocrine neoplasm imaging.

Results This article is intended to provide an overview of the available imaging procedures with their respective advantages and disadvantages for diagnostics and their value for the follow-up of neuroendocrine neoplasms. Recommendations for examination protocols, typical image findings, and an outlook regarding future developments are presented.

Key Points:
- Neuroendocrine neoplasms are relatively rare and represent a complex and multiform disease group. Even in metastatic disease, long-term progression-free survival is not uncommon.
- Diagnostics in neuroendocrine neoplasms use a wide range of complementary morphological and functional imaging methods.
- Adequate selection of the imaging method, examination planning and preparation of the patient are essential for exact staging and reliable follow-up.

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ZUSAMMENFASSUNG

Hintergrund Neuroendokrine Neoplasien (NEN) sind eine sehr heterogene Gruppe von Tumoren mit Expression typischer Proteine. Es wird eine große Bandbreite radiologischer und nuklearmedizinischer Methoden benötigt, um den Krankheitsverlauf adäquat einschätzen und den Patienten optimal behandeln zu können. Das Spektrum der Fragestellungen reicht von der Detektion kleinster Primärtumoren über die Dokumentation des Metastasierungsmusters und -verlaufs bis zur Beurteilung der Eignung für bestimmte invasive bzw. nichtinvasive Therapieverfahren. Hierbei ist eine exakte Befunderfassung und -quantifizierung unerlässlich.

Methode Diese Übersicht basiert auf einer umfassenden Literaturrecherche zu den unterschiedlichen Aspekten der Bildgebung neuroendokriner Neoplasien.

Ergebnisse und Schlussfolgerung Dieser Artikel soll einen Überblick über die zur Verfügung stehenden bildgebenden Verfahren mit ihren jeweiligen Vor- und Nachteilen für die Diagnostik und ihre Wertigkeit für Verlaufskontrollen neuroendokriner Neoplasien geben. Dabei werden Empfehlungen für Untersuchungsprotokolle gegeben, typische Bildbefunde dargestellt und ein Ausblick auf zukünftige Entwicklungen gegeben.

Introduction

In 1907 the pathologist Siegfried Oberndorfer described small tumors in the small intestine in 7 patients. To emphasize that these tumors were less aggressive than carcinomas, he coined the term carcinoid [1]. He is considered to be the first to describe neuroendocrine neoplasms (NEN). These epithelial or neuroectodermal tumors can occur at almost any location in the body and are defined by the presence of neurosecretory vesicles in the tumor cells that must be confirmed by the immunohistochemical detection of synaptophysin and chromogranin A in the tumor tissue.

According to the current ENETS and WHO classification, the rate of immunohistochemical Ki67 positive tumor cells or the mitotic activity of a tumor in the mitoses per mm² is used to grade tumors (see ▶ Table 1) [2, 3].

In addition to purely neuroendocrine neoplasms, there are combined neuroendocrine/non-neuroendocrine neoplasms referred to in the WHO classification from 2017 as MiNEN (mixed neuroendocrine non-neuroendocrine neoplasia).

Metastasis is extremely rare in some NENs such as those originating in the hypohysis and the parathyroid and these are therefore also referred to as adenomas. Others have unknown biological potential and metastases are significantly more common, for example, pancreatic and intestinal NENs. Neuroendocrine carcinomas (NECs) are aggressive tumors with high potential for malignancy and a poor prognosis. They are classified as small-cell and large-cell NECs. They are most common in the lung and colon.

Since the behavior of NENs is highly dependent on the organ of origin and the grading, exact diagnostics and precise nomenclature are essential. The goal of this article is to give the reader an overview of the available methods and the organ- and tumor-specific differential indication for imaging in NENs.

Epidemiology

In total, approximately 1 % of all malignancies are NENs. Register studies in the last 30 years show an annual increase in incidences of approximately 3–4 % [4, 5] and thus a greater increase rate than all other malignancies. This is attributed to better diagnostic methods and the higher level of familiarity with the diagnosis.

Gastroenteropancreatic NENs are the most common entity (up to 70 %) followed by pulmonary NENs (25 %) [4] (▶ Fig. 3). NENs at other locations such as the adrenal glands, head-neck region, the breast, the urogenital tract and the skin are comparatively rare.

48 % of NENs have already metastasized to the local surroundings and 27 % to other organs at the time of diagnosis [4], with the rate of metastasis increasing with a higher WHO grade (21 % for G1, 30 % for G2 and 50 % for G3 tumors) and being highly dependent on the primary tumor location [6]. NENs of the stomach, duodenum, appendix, and rectum are seen more often in the localized stage, while NENs of the lung, pancreas, and small intestine are diagnosed more frequently in stages with distant metastases [7]. A primary tumor cannot be detected in approximately 8 % of all patients diagnosed with metastases.

▶ **Table 1** Currently valid grading of neuroendocrine neoplasms [1]. The Ki67 index is the most important parameter. The mitotic index is optional. According to the current ENETS definition, the term NET G3 is only valid for pancreatic tumors. Despite the Ki67 index of > 20 %, there is good histological differentiation and a correspondingly better prognosis here. Neuroendocrine carcinomas are classified as small-cell and large-cell NECs.

well differentiated NENs	Ki67 index	mitotic index
neuroendocrine tumor (G1)	< 3 %	< 2/10 HPF
neuroendocrine tumor (G2)	3–20 %	2–20/10 HPF
neuroendocrine tumor (G3) (pancreas)	> 20 %	> 20/10 HPF
poorly differentiated NENs		
neuroendocrine carcinoma (NEC) (G3)	> 20 %	> 20/10 HPF

Neuroendocrine neoplasms occur sporadically but also in connection with genetic tumor syndromes, so-called multiple endocrine neoplasms, and phakomatoses.

The relative 5-year survival rate is 95.6 % for localized NETs of the gastrointestinal tract, 86.5 % for locally advanced NETs, and 52.4 % for NETs with distant metastases [5]. The NEN-specific 5-year, 10-year, and 20-year survival rates are 91.3 %, 86.1 %, and 77.1 %, respectively. Significantly better survival rates are thus achieved than in the case of gastrointestinal carcinomas which have a specific 5-year survival rate of 53 %. Due to the low probability of metastasis, appendix carcinoids have the best prognosis with a median overall survival of over 30 years, while NENs of the pancreas and bronchus have a poor median survival of 22 and 25 months, respectively [7]. In the metastasis stage, NENs of the lung and colon have the worst median overall survival times of 6 and 4 months, respectively, due to the often worse differentiation [4].

Clinical presentation

Tumors that are not functionally active

The majority of NENs are not characterized by specific symptoms of hormone secretion. They are found as incidental findings or cause local symptoms that cannot be attributed to hormone secretion. This includes mechanical complications like impairment of intestinal motility, bleeding complications, fractures, and cholestasis as well as nonspecific symptoms of metastasis like pain and weight loss.

Tumors that are functionally active

Functionally active NENs are characterized by the secretion of hormones or biogenic amines. Details regarding the characteristic symptom constellations are provided in ▶ Table 2. The most common location of functionally active NENs is the upper gastrointestinal tract and the pancreas. For example, the gastrinoma is found in 90 % of cases in the so-called gastrinoma-triangle between the

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▶ **Table 2** Typical symptoms of functionally active neuroendorine neoplasms due to secretion of specific hormones.

hormone	proper name	main symptoms	comment
Serotonin	Carcinoid syndrome	flushing, diarrhea, cramping	located in the ileum, first symptomatic in the case of liver metastasis
	Hedinger syndrome	endomyocardial fibrosis, tricuspid valve insufficiency, pulmonary valve stenosis	
Insulinoma	Whipple's triad	hypoglycemia, autonomic and neurological symptoms (including tachycardia, sweating, dizziness, loss of consciousness) improvement with administration of glucose	usually benign (90 %)
Gastrin	Zollinger-Ellison syndrome	reflux, peptic ulcers, diarrhea	
Vasoactive intestinal peptide	Verner-Morrison syndrome	hypokalemia, diarrhea	
Glucagon	Glucagonoma	necrolytic migratory erythema, Diabetes	
GnRH	Acromegaly	coarsening of facial features, growth of hand/feet, macroglossia	
CRH/ACTH	Cushing's disease	adrenocortical obesity, osteoporosis, diabetes, susceptibility to infection	

porta hepatis, head of the pancreas, and duodenum. In contrast, the classic carcinoid is typically located in the ileum.

Imaging

Imaging is an important part of the primary diagnosis, staging, and follow-up of NENs since knowledge of tumor location, extent, and course have a decisive effect on treatment.

The initial examination is particularly important since the goal is to document the full extent of the disease and the anatomical positional relationship in an examiner-independent manner.

Since NENs often metastasize to multiple locations and progression often can only be observed over the course of several years, frequent follow-up examinations are required. Follow-up is challenging due to modality changes or examination at various institutions.

Ultrasound

Transabdominal ultrasound often provides the first indication of an NEN and is thus often the reason for further diagnostic workup.

If the diagnosis has already been made, ultrasound serves as a quick examination method for orientation purposes and can be used for the follow-up of prominent lesions. In one study, a sensitivity of 88 % for the detection of liver metastases was determined in a selected group of tumor patients. In the same study, the location of the primary tumor was able to be determined on ultrasound but only in approximately 1/3 of cases and thus it was significantly less sensitive than octreotide whole-body scinitigraphy, which was able to identify the primary tumor in 62 % of cases [8]. As a result of contrast-enhanced ultrasound (CEUS), the diagnostic accuracy regarding the determination of the primary tumor location, particularly in the pancreas, and the detection rate of liver metastases was able to be improved [9].

Endoscopic ultrasound is the most sensitive method for diagnosing pancreatic NENs with a sensitivity of 82–93 % and a specificity of 86–95 % [10–12]. Endoscopic ultrasound is important also for the follow-up of small pancreatic NENs occurring as part of MEN1 disease and for primary tumor search in CUP-NEN, particularly of the stomach, duodenum, and rectum.

CT

Multidetector spiral CT (MDCT) is the method of choice for the primary diagnosis of NENs due to its ubiquitous availability, examiner independence to a large extent, and high detail resolution and examination speed even in the case of large examination volumes with the possibility of multiphasic protocols.

Patient preparation and protocol selection have a major effect on the value of the examination and should therefore be performed carefully and in a manner that is adapted to the individual medical issue.

Examination protocol/patient preparation

Negative oral contrast enhancement, e. g., with approximately 1 liter of 3 % mannitol solution, that the patient consumes slowly starting approximately 1 hour before the examination, is recommended in order to be able to detect small intramural intestinal tumors also in the distal small intestine [13].

An antiperistaltic medication (e. g. butylscopolamine or glucagon) can be optionally administered to the patient prior to the examination.

Since NENs often show significant arterial contrast enhancement and often metastasize to the liver, multiphasic examinations of the upper abdomen are recommended.

The liver and pancreas should be imaged in a late arterial phase, i. e., approximately 30–35 seconds after the start of injection or 10–15 seconds after wash-in of the contrast agent in the abdominal aorta if bolus tracking is used. The scan region of the

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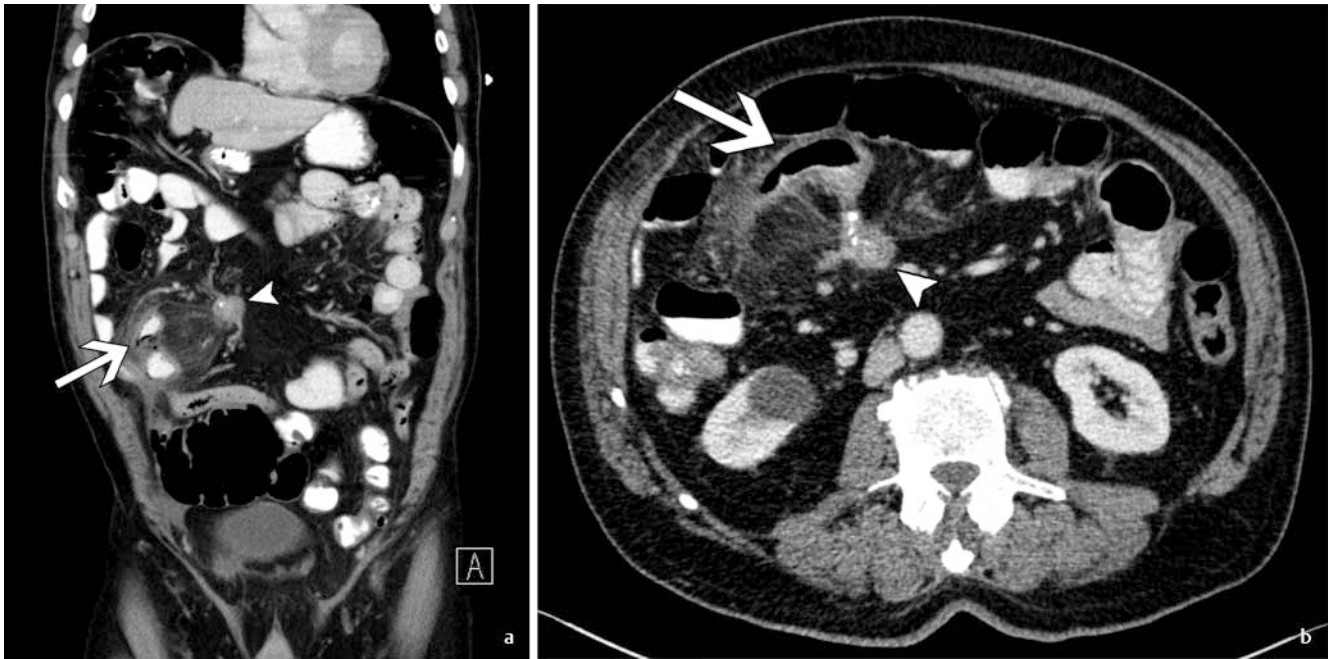
▶ **Fig. 1 a, b** 80-year-old patient with acute abdominal pain. Contrast-enhanced CT in the venous phase with positive oral contrast in coronal and axial reconstruction. Twisted, dilated, and gas-filled small bowel loops (arrow) and enlarged partly calcified mesenteric lymph node metastasis with mesenteric fibromatosis (arrow tip). The intraoperative finding of ileum segment resection showed torsion and hemorrhagic infarction of the ileal loop due to multifocal, well differentiated neuroendocrine tumor (G1) of the ileum with three lesions up to 1.2 cm with infiltration of the subserosa and a large mesenteric lymph node metastasis of 2.3 cm with perinodal growth surrounded by sclerosis with focal dystrophic calcification and with infiltration of the perineum. To date, the patient shows no sign of distant metastases.

arterial phase can be expanded in a caudal direction when searching for NENs in the small intestine.

For good contrast enhancement, a low-osmolar non-ionizing contrast agent was applied via a sufficiently large venous access with a total dose of approximately 0.3 to 0.5 g iodine/kg body weight [14] and an iodine delivery rate (IDR) of approximately 1.5 g iodine/s, ideally followed by a 30 ml bolus of a physiological saline solution.

Depending on the particular medical issue, the neck, chest, and abdomen can be examined in the late portal venous phase that occurs approximately 70 seconds after the start of injection or 50 seconds after bolus wash-in in the aorta.

In the case of isolated visualization of the neck and chest, the amount of contrast agent and the injection rates can be reduced. An arterial phase is typically not necessary here.

Typical findings

NENs of the small intestine are often associated with mesenteric fibrosis due to a desmoplastic reaction around local lymph node metastases. It results in typical partially calcified fibromatosis of the mesentery, which can cause vessel encasement with impaired vascularization and impaired motility of the intestinal loops. These lesions are often an indication of a tumor of the lower small intestine even when direct detection of a primary tumor is not successful (see ▶ **Fig. 1**).

In contrast to pancreatic carcinomas, NENs of the pancreas often show arterial hypervascularization or a partial or complete cystic appearance. It is possible to confuse them with adenocysto-

mas, cysts, or IPMNs. In the case of solid hypervascularized pancreatic lesions, intrapancreatic accessory spleen and metastases of an NEN in another primary location should be considered as a differential diagnosis. Largely cystic tumors have a slightly better prognosis [15] (see ▶ **Fig. 2**).

Since gastric, duodenal, and rectal NENs are often diagnosed via endoscopy or endoscopic ultrasound, CT imaging is often limited here to local staging and the search for metastases in advanced tumors.

Diagnostic performance

One study from the year 2010 showed that the sensitivity of all imaging methods (CT, MRI, nuclear medicine) for liver metastases of NENs is poor compared to histological hemihepatectomy specimens due to the presence of numerous micrometastases and that far fewer than half of all liver metastases are found with each method [16]. However, since all other studies compare the methods to one another, data regarding detection rates, sensitivities, and specificities can only be considered in context with the reference method which also has only limited validity.

Compared to the clinical course and to PET, CT showed good average sensitivity and specificity of 82 % and 86 %, respectively, for the detection of gastroenteropancreatic or pulmonary NENs [17, 18] and 84 % and 92 %, respectively, for the detection of liver metastases [8, 19]. The average sensitivity of 61 % for the detection of bone metastases was only moderate with a specificity of 99 % [20].

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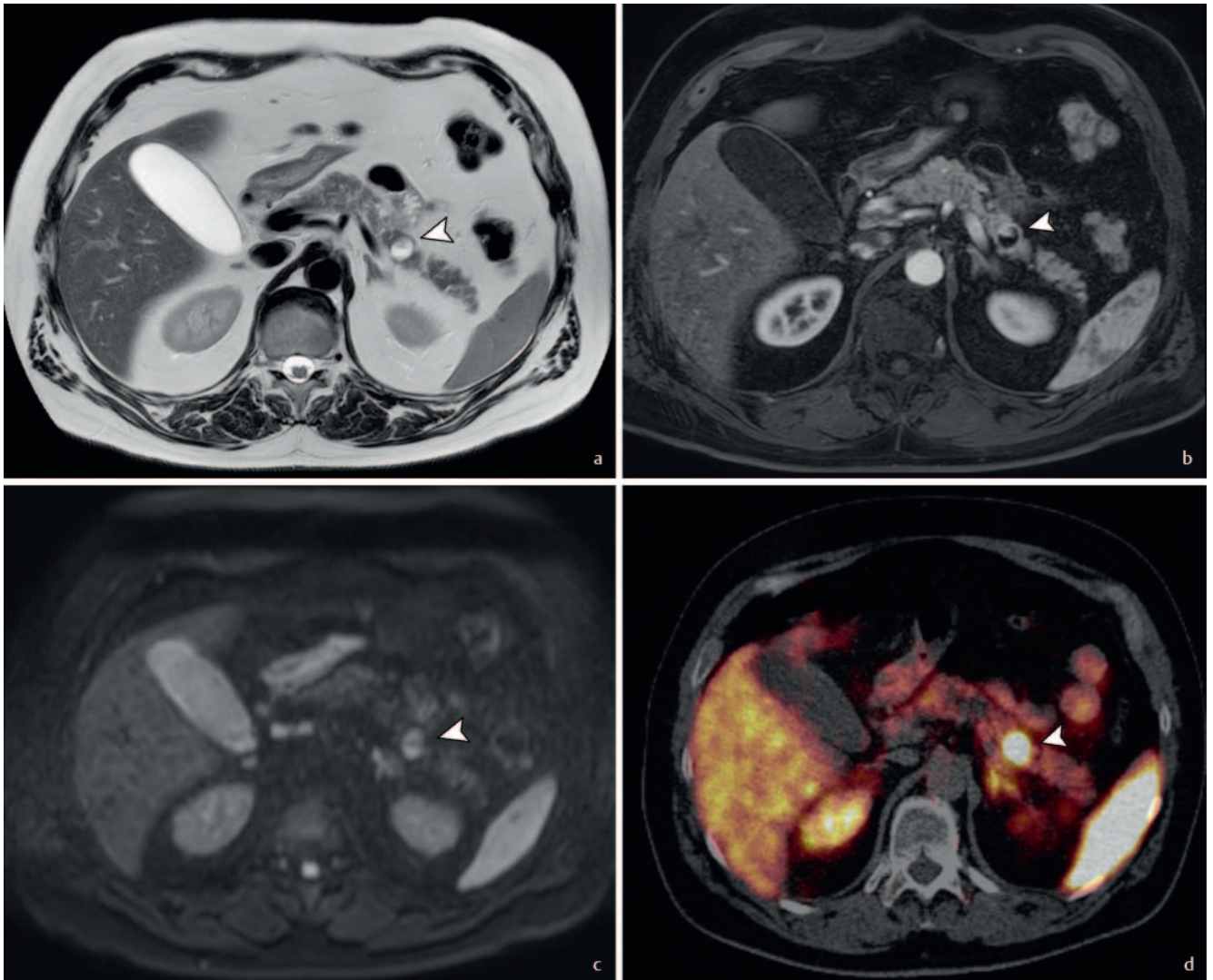
▶ **Fig. 2** 52-year-old patient with an incidental finding of a cystic pancreatic lesion in the tail of the pancreas **a**. Early arterial enhancement of the periphery of the cyst and a solid portion within the cyst **b**. The diffusion weighting at b = 800mm²/s shows a significantly increased signal **c**. Ga68-Dotatoc-PET/CT shows signs of clear somatostatin receptor expression **d**. The histological finding after pancreatic left resection showed a G1 glucagonoma.

The detection rate of CT for NENs of the pancreas is best in the late arterial phase and worst in the portal venous phase. Dynamic perfusion CT examinations promise a more precise diagnosis. In 2011, it was able to be shown in a small patient population that strong arterial contrast enhancement followed by clear washout has a PPV of 75 % and an NPV of 100 % for an NEN [21]. Since blood flow and intratumoral blood volume correlate with the degree of microvascularization, which decreases with the degree of malignancy, perfusion CT provides prognostic information in NENs of the pancreas [22].

The average sensitivity and specificity of CT enteroclysis for the detection of tumors of the small intestine are 50–85 % and 25–97 %, respectively [23, 24], albeit with time-consuming patient preparation.

The detection of lymph node metastases is less precise with MDCT than with somatostatin receptor-specific PET-CT. Therefore, only approximately 65 % of lymph node metastases that were able to be detected on PET-CT were identified with MDCT in a comparison study [25].

The detection rate for liver metastases of NEN is worse in most studies than in the case of MRI. In the diagnosis of HCC, which is also often hypervascularized, sensitivities and specificities that are comparable to those of MRI using liver-specific contrast agent were achieved using optimized low-dose protocols [26].

The treatment effects of antiangiogenic medications or embolization of liver metastases can be monitored with perfusion measurements [27]. As already shown for HCC, perfusion parameters have prognostic relevance but not necessarily an effect on tumor volume. Therefore, they are potential independent biomarkers in the follow-up of NENs.

Computed tomography is the most sensitive method for the staging of lung metastases. Although a native low-dose examination is sufficient for orientation purposes, contrast-enhanced examination is recommended for complete evaluation of the
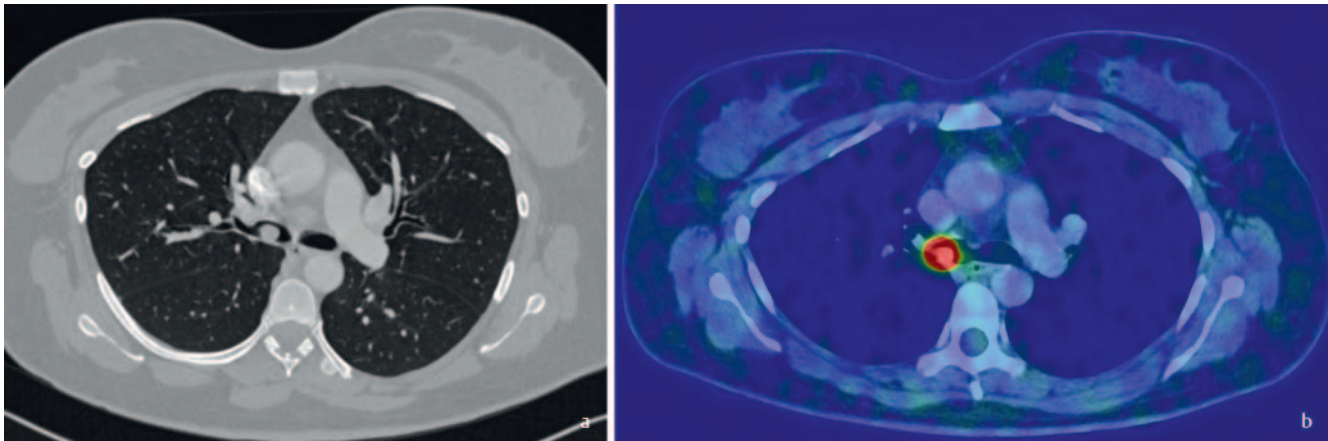
▶ **Fig. 3** CT of the lung in a 36-year-old patient who presented with intermittent hemoptysis and dyspnea. Contrast-enhanced CT **a** shows an approximately 1-cm endobronchial polypoid tumor in the right main bronchus. 68Ga-DOTATOC-PET-CT **b** shows intensive tracer uptake in the lesion. Histological workup showed a typical bronchial carcinoid (G2).
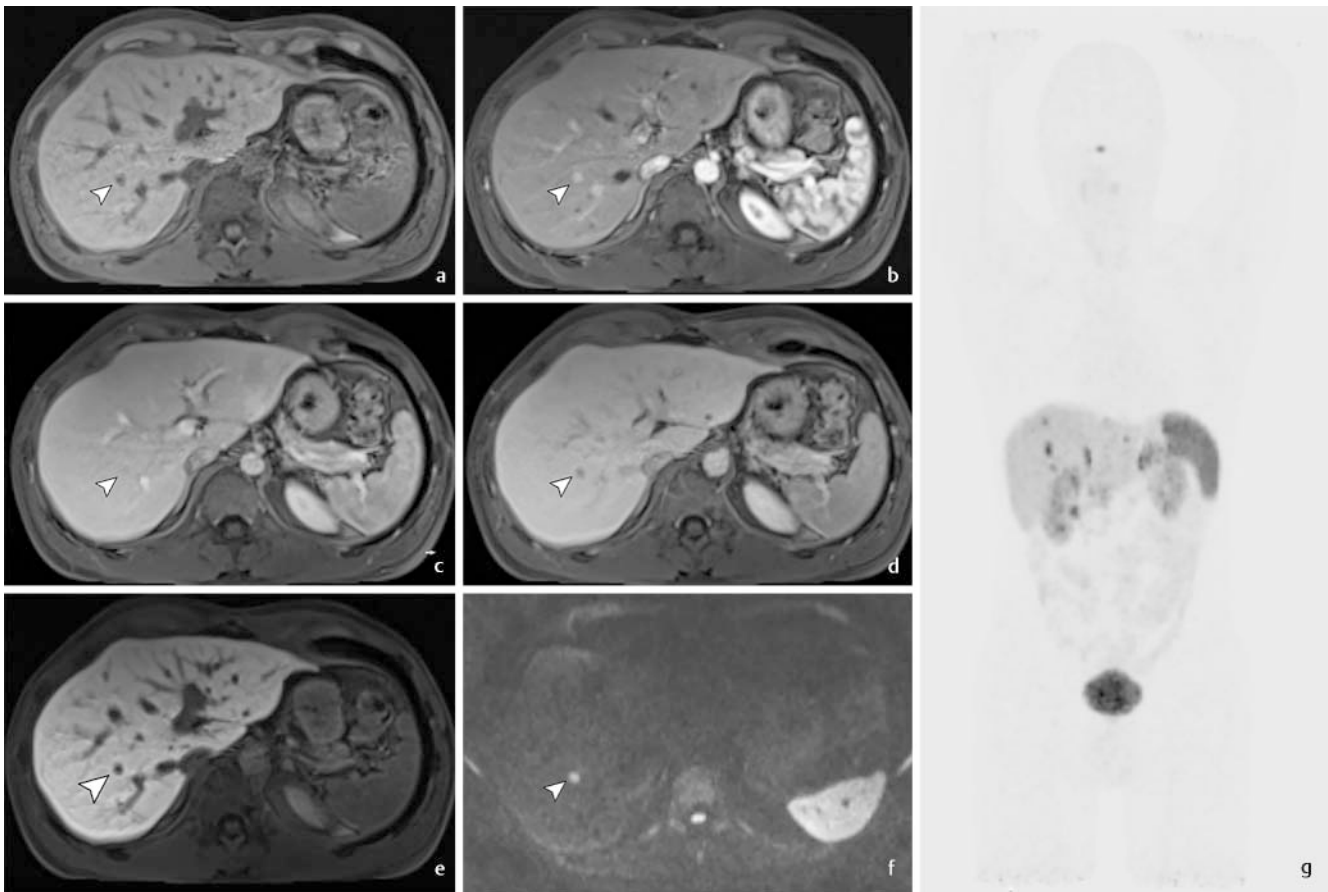
▶ **Fig. 4** Contrast-enhanced MRI of the upper abdomen with liver-specific contrast agent **a–e**), diffusion-weighted MRI **f**, and 68Ga-DOTATOC-PET-CT **g** in a 39-year-old man, who was diagnosed with a highly differentiated NET of the ileum following a subileus and primary tumor resection. 2 years later, liver metastases were detected for the first time which have since been stable for 21 years under treatment with somatostatin analogs. The image shows one liver metastasis as an example which is hypointense on the native image **a**, hyperintense in the late arterial phase **b**, and increasingly isointense compared to the liver parenchyma over the further course **c–e**. In the late phase demarcation of the metastasis due to washout and contrast enhancement in the hepatocytes. Signs of a diffusion restriction at b = 800 mm²/s **f**. The PET component of 68Ga-DOTATOC-PET-CT shows multiple additional liver metastases **g**.
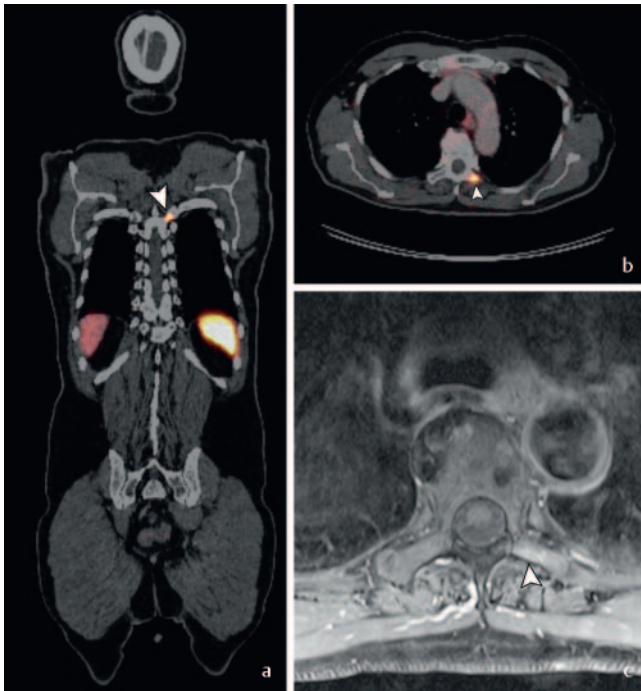
▶ **Fig. 5** Patient after complete resection of an ileum NET 11/2013 with detection of a singular metastasis in the left transverse process of thoracic vertebral body 5 (68Ga-DOTATOC-PET-CT, **a, b**) with mild contrast enhancement in the contrast-enhanced fat-saturated T1-weighted MRI sequence **c** with no other metastases.

▶ **Fig. 6** Extensive hepatic and osseous metastases of NET in carcinoid-CUP syndrome (G2). 68Ga-DOTATOC-PET-CT shows pathological somatostatin receptor expression in liver and bone metastases and physiological tracer accumulation in the hypophysis, spleen, thyroid, and bladder **a**, while 18FDG-PET-CT identifies metastases with higher biological significance due to the increased cell metabolism with lower somatostatin receptor expression (arrow, **b**).

mediastinum. If PET-CT chest examination is to be performed, the CT component should be performed using the breath hold technique to optimize the diagnostic significance [28].

Iterative image reconstruction algorithms promise a reduction of the contrast agent dose and radiation exposure while the sensitivity remains constant.
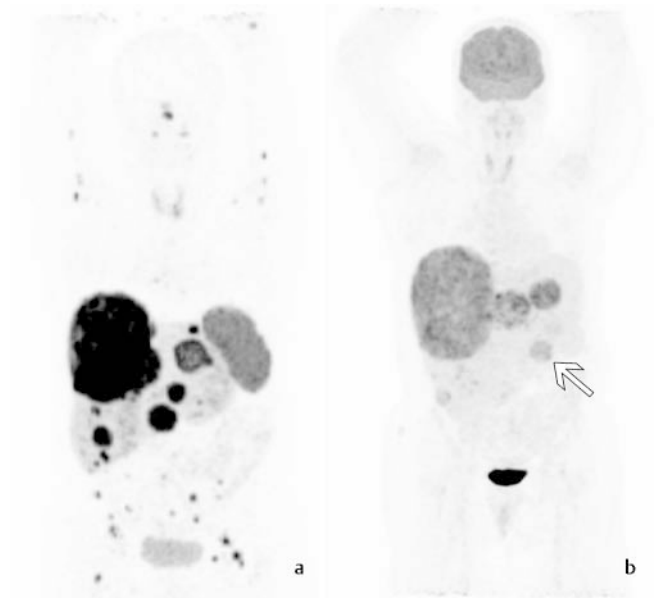
Multi-spectral CT is a technique with which substances that are similar on a standard scan can be differentiated with the simultaneous use of various X-ray spectra. Virtual native images, virtual monochromatic images for improving the contrast and iodine maps for quantifying iodine in the tissue can be calculated in this way.

Multi-spectral CT has been well studied particularly in HCC. It has also been studied for the evaluation of NENs. Therefore, for example, iodine maps can be used to increase the sensitivity for NENs of the pancreas from 67 % to 96 % [29]. Due to the high technical requirements, multi-spectral CT is not yet widely used in the clinical routine despite dose-neutral protocols.

MRI

Due to the high soft-tissue contrast, MRI is the most sensitive method for the diagnosis and follow-up of liver metastases [30] and in addition to PET-CT and endoscopic ultrasound is the most sensitive method for diagnosing a primary tumor in the pancreas. MR enterography and MR enteroclysis are superior to CT for the diagnosis of tumors of the small bowel [31].

In addition to T2 weighting, older studies recommend a T1-weighted fat-saturated sequence in the arterial phase for MRI

of the upper abdomen [30]. Liver-specific contrast agents have further optimized the sensitivity and specificity of liver metastases to 91 % and 100 %, respectively [32].

As a result of the use of respiratory gating and due to the good reproducibility, diffusion-weighted imaging (DWI) has become important for whole-body imaging. DWI is particularly sensitive for very small liver lesions. In one study, DWI yielded additional findings in almost every second patient and the total number of detected liver metastases was 78 % higher than in the case of morphological measurements [33]. It additionally allows better differentiation of cysts or hemangiomas from malignant lesions based on the apparent diffusion coefficient (ADC), which is usually lower in malignant lesions [34]. It was shown for HCC that changes in the ADC value under treatment as a sign of tumor necrosis are an independent predictor of progression-free survival [35].

In one study, DWI improved the detection rate of NENs of the pancreas compared to T1- and T2-weighted measurements from 71 % to 93 % [36]. The ADC value allows conclusions regarding the malignancy of a pancreatic lesion since it correlates negatively with the WHO grade of an NEN of the pancreas [37].

In IVIM (intravoxel incoherent motion) DWI, as a further development of DWI, a mathematical model is used instead of the ADC value to determine the true diffusion coefficient in that the capillary blood flow and the perfusion fraction are determined separately. This further refinement of the method allows more precise differentiation of pancreatic lesions regarding their perfusion. Although the measurements are not yet robust enough for broad clinical use, various benign and malignant entities of the

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pancreas can be differentiated based on individual perfusion parameters [38].

New 3 D acquisition and acceleration techniques, such as compressed sensing, allow volume measurements with acceptable spatial and high temporal resolution of a few seconds during free breathing, thus allowing the semiquantitative characterization of contrast perfusion on MRI. The sequencing technique is extremely computationally intensive and only recently became commercially available. However, to date, only initial feasibility studies are available [39, 40].

A new approach in molecular MRI imaging is chemical exchange saturation transfer (CEST) MRI in which numerous endogenous biomolecules and exogenic contrast agents can be detected with a much great signal output and resolution compared to conventional spectroscopy [41]. The method primarily originates from brain tumor imaging. The first successful attempts involving the trunk included the breast, prostate, and liver.

The highest sensitivity and specificity for liver metastases are achieved in the clinical routine with the combination of T1-weighted native scan, diffusion-weighted measurement, dynamic fat-saturated T1 sequence and a T1-weighted measurement in the hepatobiliary late phase approximately 10 minutes after injection of the liver-specific contrast agent. Due to the higher slice resolution, 3 D sequences are to be preferred for T1 measurements [42] (▶ Fig. 4).

Upon detection of NENs of the pancreas, MR cholangiopancreatography (MRCP) is additionally recommended to facilitate planning of surgical resection.

MRI with targeted distension of the small bowel in the form of MR enterography has higher sensitivity and specificity than CT for the noninvasive detection of primary tumors of the small bowel (94.4 % and 99 %, respectively, compared to 61.1 % and 95.8 %, respectively) [31]. The added benefit of the more invasive MR enteroclysis method with its need for a nasojejunal tube is controversial and the method is less widely used [43].

In MRI follow-up examinations, it is sometimes not necessary to administer contrast agent if liver metastases can be sufficiently detected without contrast agent [44].

The current guidelines recommend use of MRI, particularly when the metastasis load in the liver is to be determined for surgical planning and when follow-up of abdominal NEN manifestations is to be performed particularly in the case of a good prognosis [28].

Invasive diagnostic methods

Image-guided minimally invasive methods are important for the histological workup of unclear findings.

Due to the relatively low expense, unclear liver lesions are often primarily confirmed by transabdominal ultrasound-guided biopsy.

A biopsy or fine-needle aspiration for more precise characterization of pathological changes in the pancreas or adrenal glands, of mural processes, and of suspicious perigastric lymph nodes can be performed with the help of endoscopic ultrasound.

CT-guided biopsy is the method of choice for the histological workup of unclear lung and bone lesions. Lymph nodes can also be biopsied under CT guidance at almost any location. If suffi-

ciently visible on CT, particularly viewed in connection with additional methods, targeted biopsy of the liver is possible.

If other methods fail or suspicious lesions cannot be visualized with sufficient reliability for biopsy, MRI-guided biopsy can be performed due to the already high native soft-tissue contrast and the relatively free selection of access angles. If needed, longer contrast enhancement of the liver with a liver-specific contrast agent can facilitate biopsy confirmation [45].

Arterial stimulation tests with venous sampling can be used for invasive localization diagnosis in the case of a lack of morphological confirmation prior to surgery. Superselective arterial injection of calcium gluconate or secretin and the determination of the insulin or gastrin level in the blood in the hepatic vein have a high average sensitivity of 85 % [46] for determining the location of insulinomas or 77–89 % for gastrinomas [47].

Nuclear medicine

Scintigraphy

Nuclear medicine imaging of NENs takes advantage of tumor-specific metabolic processes which is why it is called functional imaging.

One of the mechanisms that is used is the absorption of neurotransmitter precursor molecules in characteristic neurosecretory granules.

Metaiodobenzylguanidine (MIBG) as an analog to norepinephrine is actively absorbed by NEN cells. It is labeled as ^{123}I and is used primarily for diagnosing pheochromocytomas.

The expression of specific receptors in tumor tissue is a further relevant mechanism. Receptors for somatostatin, a polypeptide that performs regulatory functions at many locations in the body, are overexpressed on the cell surface of differentiated NENs (up to 70 % in insulinomas and over 90 % in NENs of the small bowel). Five types of this receptor are known. Type 2 in particular is expressed on the surface of NENs. Approximately 70 % of insulinomas and over 90 % of NENs of the small bowel express these receptors [48].

Due to the low plasma half-life of somatostatin, the somatostatin analog octreotide is used in connection with a nuclide (^{111}In-pentetreotide, Octreoscan®) for imaging. Planar somatostatin receptor scintigraphy performed with these substances is only recommended an an alternative method if PET-CT is not available [28] because it has a lower spatial resolution and worse diagnostic value at a higher dose and significantly higher time requirement. If it is still used, SPECT in combination with CT is recommended due to the better determination of the location of suspicious lesions in such cases [49].

PET/CT

In hybrid methods, high-resolution morphological radiology examinations are acquired during a single examination almost simultaneously with functional imaging. PET-CT is the most important hybrid method for receptor-specific diagnostics in NEN imaging and has largely replaced planar scintigraphy, PET, and SPECT/CT. However, in contrast to the Octreoscan mentioned above, PET-CT is often not reimbursed by health insurance.

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The PET dataset is acquired with the help of radioactive tracers that emit positrons. ^{68}Ga bound to ligands for the somatostatin receptor is usually used for NEN imaging. ^{68}Ga-DOTATATE (DOTA-[Tyr³] octreotate), ^{68}Ga-DOTANOC (DOTA-1-Nal3-octreotide) and ^{68}Ga-DOTATOC (edotreotide, DOTA(0)-Phe(1)-Tyr(3)) octreotide) are most commonly used. Although ^{68}Ga-DOTATATE has a ten times higher affinity for somatostatin receptors in vitro, this difference was not statistically significant in in-vivo applications [50]. It should be mentioned that none of the indicated substances has been formally approved in accordance with pharmaceutical regulations.

The CT dataset is used both for morphological information and for improving the quality of the PET dataset using an attenuation correction calculated from the CT data.

Since ^{68}Ga has a short half-life of 67 minutes, the tracers must be synthesized on site.

^{64}Cu could become more important in the future as a tracer substance in connection with somatostatin analogs since it can be manufactured at a central location because of the longer half-life of 12 hours. However, like ^{18}F as a further positron-emitting tracer, it is more difficult to manufacture and results in higher radiation exposure. Initial studies show diagnostic accuracy comparable to that of tracers containing gallium [51]. An additional promising approach is the use of ^{68}Ga-DOTA-exendin, an analog of glucagon-like peptide-1, which has a high sensitivity for insulinomas [52].

If sufficient receptor population is seen, the above somatostatin analogs can be used in connection with therapeutic instead of diagnostic radionuclides like ^{177}Lu or ^{90}Y for Peptide Receptor Radionuclide Therapy (PRRT).

The glucose analog ^{18}FDG can be used as a nonspecific tracer for glucose metabolism. It can be used for highly proliferative NENs since glucose metabolism increases in the case of a high Ki67 index and somatostatin receptor expression decreases (▶ **Fig. 6**). Increased FDG uptake indicates a higher tumor grade and a significantly worse prognosis [53]. Particularly in the case of NECs, additional FDG-PET examination is therefore recommended in the current guidelines [28].

PET-MRI examinations combine the advantages of high soft-tissue contrast and the potentially multiparametric image acquisition of MRI with the advantages of PET. However, the complex attenuation correction, the issue-dependent protocol selection, and the significant time requirement for whole-body MRI imaging represent limitations here. Due to the plurality of possible sequence parameters, imaging standardization is significantly more difficult to achieve than with CT. Lung lesions are slightly more difficult to visualize than on CT.

In initial studies, MRI/PET with Dixon sequences was able to achieve tumor visualization and detection comparable to that of low-dose CT in PET-CT [54]. At present, the available data regarding PET-MRI for the imaging of NENs is still minimal, particularly regarding NENs metastasized to the pancreas and liver. However, advantages can be assumed as a matter of principle.

Follow-up

The recommendations of the European and American professional societies regarding the frequency of follow-up imaging vary but typically recommend follow-up intervals of 6–12 months or 3 months in the case of highly proliferative tumors. In the case of complete tumor resection and a lack of metastases, a follow-up period of at least 10–15 years is recommended or lifelong monitoring in the case of intestinal tumors. Follow-up is not necessary only in the case of R0-resection of G1 NENs of the appendix with a size of less than 1 cm due to the low risk of metastases. In the case of R0-resection of small NENs of the rectum, a single endoscopic follow-up examination is sufficient.

The selection of the method is not precisely defined and depends on patient age, pattern of metastasis, and course of the disease. The strengths and weaknesses of the individual modalities must be taken into consideration here (see ▶ **Table 3**). However, CT and MRI are the primary methods for routine staging due to their availability and reproducibility. Functional whole-body imaging such as somatostatin receptor imaging is recommended at greater intervals of approximately 2–3 years [28].

Documentation of the findings is very important. Comparison with the most recent prior examination is often not sufficient due to the low dynamics of the findings. Even outside of studies, it is useful to evaluate the course of the disease on cross-sectional images according to defined criteria. RECIST 1.1 for example is broadly used and accepted but has limitations in slow-growing and cystic or necrotic tumors. Since purely diameter-based measurements are also highly dependent on the contrast phase and the modality and new targeted therapies do not necessarily result in a change in size, modifications to the response criteria that are relevant for evaluating prognosis in the case of HCC [55] and GIST [56] have been proposed. However, for NENs, the modified response criteria have not yet shown an advantage over the RECIST criteria for prognosis assessment [57].

Summary

Due to their varied clinical picture and at times protracted course, neuroendocrine neosplasms represent a challenge for imaging. The selection of the method and the care given to the evaluation have a major effect on the treatment and course of the disease. Therefore, complete and exact staging can only be achieved by combining the strengths of the various methods.

Due to its good availability, ultrasound can pave the way for primary diagnosis and provide a quick impression of the course of the disease. Endoscopic ultrasound can detect the smallest intramural tumors in the upper and lower gastrointestinal tract or pancreatic lesions.

Due to its high temporal and spatial resolution with simultaneous detection of large volumes, CT is essential for primary staging. As a result of techniques like dual-energy CT, significant advances in diagnostic accuracy at a constant or reduced dose have been able to be achieved.

The good soft-tissue contrast of MRI is highly advantageous for the evaluation of parenchymatous organs of the upper abdomen.

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▶ **Table 3** Overview of advantages and disadvantages of individual imaging methods and their use in NEN diagnostics.

method	advantages	disadvantages	application area
(endoscopic) ULTRASOUND	Availability, high sensitivity of endoscopic ultrasound for intramural tumors in the upper and lower gastrointestinal tract and pancreas	poor reproducibility thus not suitable for objective follow-up, primary tumor screening using transabdominal ultrasound often not successful	primary diagnosis, tumor screening in the stomach, pancreas, and rectum via endoscopic ultrasound, intermediate staging Biopsy
CT	availability, speed, large volume can be visualized, multiphasic protocols to perfusion measurements	radiation exposure, contraindications to contrast agent, low native soft-tissue contrast, imprecise for lymph node metastases	tumor screening, primary staging, follow-up (particularly chest and bone)
MRI	high native soft-tissue contrast, varying levels of contrast, no ionizing radiation	lower speed, limited suitability for lung imaging, contraindications like claustrophobia and electronic implants	primary tumor screening particularly in the pancreas, follow-up of liver metastases
PET-CT	location of molecules (functional method), high sensitivity for small lesions	limited availability and high cost, radiation exposure	primary tumor screening, screening for small distant metastases (▶ **Fig. 5**), screening for lymph node metastases, treatment stratification regarding receptor-specific therapies

The lack of radiation is advantageous for regular follow-up particularly of younger patients with a good prognosis. With diffusion weighting, perfusion measurements, and developments in molecular imaging, MRI is increasingly capable of providing morphological information as well as functional parameters regarding tissue characterization.

Nuclear medicine methods and hybrid methods such as PET-CT provide additional functional information that can be used not only to detect the smallest metastases or primary tumors but can also significantly affect therapeutic decisions on the basis of biochemical tumor profiles.

It is to be expected that future tumor classifications and response criteria will include prognosis-relevant morphological and functional biomarkers that go beyond basic size measurement to find customized treatments for a better outcome particularly in the highly heterogeneous group of neuroendocrine neoplasms.

Conflict of Interest

The authors declare that they have no conflict of interest.

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