The Status of Neuroendocrine Tumor Imaging: From Darkness to Light?

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Key Words

Neuroendocrine tumors · Imaging · Computed tomography · Magnetic resonance imaging · Scintigraphy · Positron emission tomography

Abstract

Diagnostic imaging plays a pivotal role in the diagnosis, staging, treatment selection and follow-up for neuroendocrine tumors. The available diagnostic strategies are morphologic imaging, including computed tomography, magnetic resonance imaging (MRI) and ultrasound techniques, and molecular imaging, including scintigraphy with ¹¹¹In-pentetreotide and positron emission tomography with ⁶⁸Ga-DOTA-peptides, ¹⁸F-DOPA and ¹¹C-5-HTP. A combination of anatomic and functional techniques is routinely performed to optimize sensitivity and specificity. The introduction of diffusion-weighted MRI and dynamic contrast-enhanced techniques represents a promising advance in radiologic imaging, whereas new receptor-binding peptides, including somatostatin agonists and antagonists, represent the recent most favorable innovation in molecular imaging. Future development includes the short-term validation of these techniques, but in extension also a more comprehensive multi-level integration of biologic information pertaining to a specific tumor and patient, possibly encompassing genomic considerations, currently evolving as a new entity denoted 'precision medicine'. The ideal is a diagnostic sequence that

captures the global status of an individual's tumor and encompasses a multidimensional characterization of tumor location, metabolic performance and target identification. To date, advances in imagery have focused on increasing resolution, discrimination and functional characterization. In the future, the fusion of imagery with the parallel analysis of biological and genomic information has the potential to considerably amplify diagnosis.

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Introduction

Neuroendocrine tumors (NETs) represent a considerable diagnostic challenge as their clinical presentation is protean, nonspecific and usually late, often when hepatic metastases are already evident [1]. In their diagnostic workup, two critical issues are present: firstly, the need to identify tumor presence and, secondly, to define the primary location and assess regional and distant metastases. Plasma biomarkers and imaging have been used to define these areas. This includes molecular imaging techniques to acquire information on the tumor's somatostatin receptor (SSR) expression [SSR scintigraphy (SRS)] and metabolic status [¹⁸fluorodeoxyglucose-positron emission tomography (¹⁸FDG-PET)] and histopathological examination of tumor biopsies, including immunohistochemistry, providing further information,

Fig. 1. Venn diagram of modalities involved in the identification of a NET. ^{111}In -OCT = ^{111}In -pentetreotide scintigraphy; ^{68}Ga -PET = PET with ^{68}Ga -DOTA-peptides; ^{18}F -DOPA = ^{18}F -dihydroxyphenylalanine; ^{11}C -5-HTP = ^{11}C -5-hydroxy-L-tryptophan; FNA = fine-needle aspiration; FNB = fine-needle biopsy; CTC = circulating tumor cells.

for example, on its proliferative activity (Ki67). Current biomarkers such as chromogranin-A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) are, however, generally accepted as suboptimal in terms of sensitivity and specificity [2]. The recent demonstration of specific NET transcripts in whole blood suggests that this strategy may enable early diagnosis and detection of lesions and may provide a basis for prognostic determination and therapeutic recommendation [3]. The currently evolving research area denoted ‘precision medicine’, by which, for example, correlations between genomics and image findings may be established, is resource demanding but holds great potential.

Imaging plays a pivotal role in diagnosis, staging, treatment selection and follow-up of NETs (fig. 1). Current diagnostic methods include morphologic modalities such as computed tomography (CT), magnetic resonance imaging (MRI), transabdominal ultrasound (US), endoscopic US (EUS) and intraoperative US (IOUS). Nuclear medicine imaging or molecular imaging consists of scintigraphy including single photon emission computed tomography (SPECT) with ^{111}In -pentetreotide or, more recently, PET with ^{68}Ga -labeled somatostatin analogs (SSA), ^{18}F -DOPA and ^{11}C -5-HTP [1]. Because of the large variability between NETs in, for instance, proliferation rate (Ki67) and SSR subtype profile,

no modality alone is entirely effective and, overall, these exhibit a sensitivity and specificity of ~80–90% [4] (fig. 2). A combination of anatomic and functional techniques is routinely performed to optimize sensitivity and specificity and thereby maximize the acquisition of clinically relevant information [5, 6]. This has been facilitated by the development of current hybrid scanners (SPECT/CT and PET/CT), whereby functional image findings may be directly correlated to morphology and vice versa. In disseminated disease, the tumor’s SSR status is generally assessed by ^{111}In -pentetreotide scintigraphy or ^{68}Ga -SSA-PET/CT in order to also evaluate the patient’s eligibility for peptide receptor radionuclide therapy (PRRT). This assessment was previously a prerequisite, also before starting systemic treatment with unlabeled SSA, but this routine has during the last few years been questioned.

The major unmet need in NET imaging is, however, the development of more inclusive criteria for therapy monitoring that apply to slow-growing tumors and allow the validation of the more recent functional techniques (MRI and PET) as well as integrate biologic and metabolic information (table 1) [3, 7]. This article assesses the strengths and limitations of current imaging approaches for NETs and describes the future perspectives using a SWOT analysis structure.

Fig. 2. Methods for the identification of primary and metastatic gastroenteropancreatic NETs. Data are pooled from 52 studies and are mean (95% confidence interval). Data for specificity and sensitivity are not comparable across studies. S = Calculated sensitivity.

Table 1. The role of morphologic and molecular imaging techniques in NETs

	Primary	Localization	Staging	Restaging	Therapy selection	Modification of management
GEP	Pancreas (functional) ^a	SRI [21, 47, 114, 115] EUS [1, 8] CT/MRI [8, 116] ^{11}C -5-HTP [26]	SRI + CT/MRI [5, 6] ^{11}C -5-HTP [26]	SRI + CT/MRI [5, 6] ^{11}C -5-HTP [26]	SRI: SSA, PRRT [48] CT/MRI: surgery [1]	SRI [47, 57] FDG [29]
	Pancreas (nonfunctional)	EUS [1, 8] SRI [17, 21, 115, 117] CT/MRI [8, 116]	SRI + CT/MRI [5, 6] ^{11}C -5-HTP [26]	SRI + CT/MRI [5, 6] ^{11}C -5-HTP [26]	SRI: SSA, PRRT [48] CT/MRI: surgery [1]	SRI [47, 57] FDG [29]
	Duodenum	SRI [21, 114, 115] EUS [1]	SRI + CT/MRI [5, 6] ^{11}C -5-HTP [26]	SRI + CT/MRI [5, 6] ^{11}C -5-HTP [26]	SRI: SSA, PRRT [48] CT/MRI: surgery [1]	SRI [47, 57] FDG [29]
	Small bowel	SRI [17, 117–119] video-capsule DB enteroscopy [120] CT [8]	SRI + CT/MRI [5, 6] ^{18}F -DOPA [58]	SRI + CT/MRI [5, 6] ^{18}F -DOPA [58]	SRI: SSA, PRRT [48] CT/MRI: surgery [1]	SRI [117] FDG [29]
	Gastric	EUS [8] SRI [121] CT [121]	SRI + CT/MRI [5, 6]	SRI + CT/MRI [5, 6]	SRI: SSA, PRRT [48] Endoscopy: resection [121]	
	Colon	EUS [8] SRI [121] CT [121]	SRI + CT/MRI [5, 6]	SRI + CT/MRI [5, 6]	Endoscopy: resection [121] SRI: SSA, PRRT [48] CT: surgery [1]	SRI [57] FDG [29]
	Rectum	EUS [8] SRI [121] CT/MRI	SRI + CT/MRI [5, 6]	SRI + CT/MRI [5, 6]	SRI: SSA, PRRT [48] CT: surgery [1] Endoscopy: resection [1]	SRI [57] FDG [29]
Bronchial	Bronchia	Bronchoscopy [120] SRI [122]	SRI [123] CT [123] FDG [124]	SRI [123] CT [123] FDG [124]	Bronchoscopy: resection [120] CT (MRI): surgery [123] SRI: SSA, PRRT [48]	SRI [57] FDG [29]
Unknown	Unknown	SRI [125]	SRI + CT/MRI [5, 6]	SRI + CT/MRI [5, 6]	SRI: SSA, PRRT [48] CT: surgery, locally directed ablative therapies [121]	SRI [57] FDG [29]

GEP = Gastroenteropancreatic; SRI = somatostatin receptor imaging with either ^{111}In -pentetreotide or PET/CT with ^{68}Ga -DOTA-SSA; DB enteroscopy = double-balloon enteroscopy. ^a Except for insulinoma.

Techniques

(1) US: Transabdominal US is often the first technique utilized for NET imaging. This is simply based upon its noninvasiveness and utility. Its efficacy is, however, low. US allows for easy guidance of the biopsy needle for fine-needle aspiration cytology or core biopsy for histopathological examination. Improved techniques, including contrast-enhanced US (CEUS), EUS and IOUS have allowed for an increase in sensitivity.

(2) CT/MRI: Primary NETs are usually identified using conventional imaging with intravenously contrast-enhanced CT and MRI which are also the principal methods used for the detection of the primary tumor, describing its local extent, staging of locoregional and distant metastases, as well as for the assessment of therapeutic response. Contemporary CT utilizes multidetector (MDCT) scanners, while MRI employs a field strength of at least 1.5 T and currently includes many signal sequences to increase tissue contrast and facilitate tissue characterization. Unless contraindicated, for instance because of impaired kidney function, both CT and MRI of the liver and pancreas should be performed as multiphasic studies before and during intravenous contrast enhancement in the late arterial (portal venous inflow) and venous (portal-venous) phases [8]. Since neuroendocrine lesions and their metastases are usually hypervascular, they enhance in the late arterial phase after contrast medium injection on CT and MRI. The variations in this aspect are large and it is fairly common also with hypovascular metastases that are best delineated in the venous contrast enhancement phase. Occasionally, the patient may harbor both hypervascular and hypovascular liver metastases. The sensitivity for pancreatic NETs ranges from 69 to 94% for CT, 74 to 94% for MRI and is >80% for EUS coupled with biopsy [8–13]. The sensitivity for locating a primary small intestine NET is 100% for CT enteroclysis and 86–94% for MRI [14–16].

(3) Nuclear medicine imaging or molecular imaging: These techniques provide information for establishing the SSR status (^{111}In -pentetreotide), metabolic activity (^{18}F FDG) and specific amine or peptide regulatory profile (e.g. ^{18}F -DOPA). In addition, they generally provide further details in respect of the extent of disease and thereby facilitate more accurate staging and precise therapy.

(a) The radiolabeled SSA ^{111}In -pentetreotide is the most commonly used agent for SRS. Examination comprises two-dimensional planar imaging and three-dimensional SPECT at 4, 24 and optionally at 48 h after injection according to recommended protocols [17].

With the increasing use of SPECT/CT, allowing for anatomical correlation of the SPECT findings, the need for the 4- and 48-hour examinations is, however, generally low. The sensitivity of ^{111}In -pentetreotide scintigraphy has been well documented and is generally >75% for gastroenteropancreatic and bronchial tumors [18]. Since 2000, the approach to the molecular imaging of NETs has been revolutionized by the introduction of PET with the ^{68}Ga -labeled octreotide derivatives DOTATOC, DOTATATE and DOTANOC (^{68}Ga -SSA-PET/CT) [19, 20]. The overall sensitivity of ^{68}Ga -SSA-PET/CT for NETs is >90%, while the specificity ranges from 92 to 98% [21–23]. Recently, ^{64}Cu -labeled SSA has also been tested for PET/CT of NETs [24].

(b) Alternative PET tracers: These include ^{18}F -DOPA, which measures neuroendocrine metabolism. This is a substrate utilized in the catecholamine synthesis pathway and is stored in the secretory granules [25]. In research centers, ^{11}C -5-HTP, a serotonin precursor, which is the substrate for aromatic L-aminoacid decarboxylase, is also utilized [26]. ^{18}F FDG-PET is usually not considered a primary diagnostic tool in well-differentiated NETs because of its low sensitivity. ^{18}F FDG PET may instead be considered for imaging of high G2 NETs with Ki67 >15–20% for which SRS and ^{68}Ga -SSA-PET/CT may be unreliable [27]. ^{18}F FDG-PET is generally recommended for neuroendocrine cancer G3 tumors, although it has been reported as positive in 57% of G1 and 66% of G2 NETs [28]. In addition, the increased glucose metabolism, expressed as standardized uptake value (SUV), can provide predictive information in terms of overall survival and progression-free survival (PFS) [29]. In particular, NETs that exhibited increased metabolic activity had a significantly lower disease control rate (100 vs. 76%) and PFS (32 vs. 20 months) after PRRT compared to ^{18}F FDG-negative tumors [28]. Recent study has shown the possibility of a three-tier metabolic grading system based on the tumor-to-background ratio of uptake of FDG as an independent prognostic marker [30].

Technique Strengths

Morphologic Imaging

Anatomic techniques are the primary imaging modalities used in the initial phase of the diagnostic workup to detect primary tumors, delineate the extent of metastatic disease, determine therapeutic strategy (particularly the margins of operability) and assess the therapeutic response (table 2a).

Table 2. Strengths of anatomic (a) and molecular imaging (b) techniques**a** Anatomic imaging

	MDCT	MRI	US techniques
Technical points	High spatial resolution (2–4 mm or below)	High spatial resolution (2–4 mm)	Absence of radiation exposure
	Multiplanar imaging	High soft-tissue contrast	
	Volume rendering	Multiplanar imaging	
	High sensitivity for small-bowel lesions (CT enterography)	Volume rendering	
		Absence of radiation exposure	
Clinical points	Initial assessment, localization, staging, restaging and definition of margins for operability	Localization, staging, restaging, definition of margins for operability and problem-solving technique	Abdominal US: biopsy guidance for liver/abdominal lesions
	High sensitivity for pulmonary, hepatic and brain lesions	High sensitivity for pancreatic and hepatic lesions	CEUS: possible characterization of dubious lesions at CT/MRI
	Availability, rapidity and reproducibility	Reproducibility	EUS: high sensitivity for pancreatic NETs, guidance for biopsy
	Independency of body habitus and extent of disease	Visualization of the biliary and pancreatic ducts (cholangiopancreatic MRI)	IOUS: delineation of liver and pancreatic lesions before resection
	Biopsy guidance for thoracic lesions	Use of organ-specific contrast media	

b Molecular imaging

	¹¹¹ In-pentetreotide	⁶⁸ Ga-peptides	¹⁸ F-DOPA	¹¹ C-5-HTP	¹⁸ FDG
Technical points	Whole-body technique	Whole-body technique	Whole-body technique	Whole-body technique	Whole-body technique
	Multiplanar imaging	High spatial resolution (4–6 mm)	High spatial resolution (4–6 mm)	High spatial resolution (4–6 mm)	High spatial resolution (4–6 mm)
	Possibility of coregistration with high-resolution CT	Multiplanar imaging and coregistration with CT	Multiplanar imaging and coregistration with CT	Multiplanar imaging and coregistration with CT	Multiplanar imaging and coregistration with CT
	Approved radiopharmaceutical for NET imaging	Single-day procedure	Single-day procedure	Single-day procedure	Single-day procedure
		Semiquantification of uptake (SUV)	Semiquantification of uptake (SUV)	Semiquantification of uptake (SUV)	Semiquantification of uptake (SUV)
Clinical points	Localization, staging, restaging and therapeutic indications	Localization, staging, restaging and therapeutic indications	Localization, staging, restaging and study of neuroendocrine metabolism	Localization, staging, restaging and study of neuroendocrine metabolism	Prognostic evaluation
	High sensitivity for lesions ≥1 cm, including difficult or unexpected sites	High sensitivity, including difficult or unexpected sites	High sensitivity, especially for carcinoids	High sensitivity, especially for pancreatic NETs	Imaging of high G2 and G3 tumors
		Possibility of labeling the same peptide used for PRRT	Alternative or a problem-solving tool when SRI is negative	Alternative or a problem-solving tool when SRI is negative	

Multidetector Computed Tomography

MDCT is the standard morphologic modality for NET imaging due to its high spatial resolution, generally <1 mm with recent MDCT scanners [31]. MDCT can localize the primary tumor, assess the extent of disease, characterize the architectural relationships with the surrounding structures and be used to reassess the disease following treatments [8, 32–34].

The multiplanarity of this technique (transaxial, coronal, sagittal and curved planes can be reconstructed) and the three-dimensional maximum intensity projection and volume rendering techniques, which delineate the organ and vascular anatomy in 3D, improve accuracy and image interpretation [7, 11, 35]. MDCT is reproducible and allows for comparison between baseline and follow-up images, irrespective of the body habitus and extent of disease. CT is the method of choice to guide the biopsy of thoracic lesions.

Magnetic Resonance Imaging

MRI has the advantage of a fairly high spatial resolution (2–4 mm), which is amplified by examination at a higher field strength in a 3-tesla scanner [36]. Optionally, the higher field strength may instead be utilized to shorten the acquisition time. The better soft-tissue contrast of MRI, as compared to CT, is particularly useful to detect liver metastases for which MRI represents the most sensitive technique [37, 38]. The soft-tissue contrast can be further increased by the use of liver-specific and superparamagnetic contrast media [34, 39]. Three-dimensional acquisition allows for viewing in multiple anatomical planes to enable accurate image interpretation. In addition, the absence of radiation exposure renders MRI the technique of choice especially in the young or those with long-standing disease who require repeated assessments [7, 11, 34].

MRI has similar indications as CT and, due to availability and costs as well as its optimal interobserver agreement, it is generally used as a problem-solving technique [37, 40]. MRI is particularly advantageous in localizing primary pancreatic tumors and for staging and restaging liver lesions [37]. Moreover, cholangiopancreatic sequences (magnetic resonance cholangiopancreatography), directed at studying the involvement of the biliary and pancreatic ducts, are useful for surgical planning and should always precede resection of a pancreatic NET [8, 41].

US Techniques

US is the modality used to guide liver and other abdominal biopsies. The absence of radiation exposure makes it a highly repeatable technique. Despite the gen-

erally low sensitivity among anatomic modalities in localizing NETs (13–27%) [42, 43], improved techniques, including CEUS, EUS or IOUS, show better performance. EUS is the most advantageous modality to detect pancreatic NETs, with pooled sensitivity and specificity of 87 and 98%, respectively, in a systematic review [44], and it represents a guide for fine-needle aspiration cytology or core biopsy [45]. Finally, the juxtaposition of the probe, during IOUS, facilitates the study of the liver and the pancreas [1] and is generally recommended in connection with resection of liver metastases and pancreatic NETs, especially in multiple endocrine neoplasia patients.

Molecular Imaging

Besides localization, staging and restaging of primary and metastatic tumors, molecular imaging allows for the functional characterization of lesions and the therapy selection with cold or radiolabelled SSA (PRRT). Functional imaging has a clinical impact in terms of modification of the therapeutic strategy and of prognosis (table 2b).

¹¹¹In-Pentetreotide

This is the only universally approved radiopharmaceutical for NET imaging. A ^{99m}Tc-labeled compound (^{99m}Tc-EDDA/HYNIC-TOC) is registered in Poland and commercially available in some European countries [46]. The use of ¹¹¹In-pentetreotide to localize, stage, restage as well as provide therapeutic indications was a major advance in NET management [5, 47, 48]. An optimal protocol, including three-dimensional reconstructed SPECT images and, possibly, high-resolution CT coregistration (SPECT/CT), ensures good image quality and provides useful clinical information, as a whole body technique, and accurate image interpretation [17]. ¹¹¹In-pentetreotide modifies the therapeutic strategy in up to 50% of cases [47, 49, 50] and can predict the response to cold or radiolabeled analogues [48].

⁶⁸Ga-SSA-PET/CT

This provides several advantages over conventional scintigraphy. These include the simple and economical synthesis of the radiopeptide from an on-site ⁶⁸Ge/⁶⁸Ga generator eluate, the single-day procedure, the possibility of semiquantification of the activity in a given region of interest as the ‘SUV’, the higher spatial resolution with the detection of 4- to 6-mm lesions and, finally, the better dosimetry [51]. The intrinsic multiplanarity of the PET techniques and the coregistration with high-resolution

CT produces low-dose, or preferably, diagnostic contrast-enhanced scans, with an improved accuracy and image interpretation [52].

Another advantage is the possibility of labeling and imaging the same peptide used for PRRT [22, 53]. ^{68}Ga -SSA-PET/CT has demonstrated a higher sensitivity than metabolic tracers, such as ^{18}F -DOPA and ^{11}C -5-HTP, and is able to sensitively visualize difficult areas including bones, peritoneum, the heart or soft tissues [54, 55]. It allows for localization, staging and restaging and provides therapeutic indications based on tumor SSR expression [21, 51, 56]. Moreover, it is able to modify the therapeutic management in >50% [56, 57].

PET with ^{18}F -DOPA

This can be of value as an alternative or problem-solving tool when SSR imaging is negative or in assessing response to treatment [51]. The sensitivity of this method is higher for carcinoids given their propensity for amine metabolism [58, 59].

PET with ^{11}C -5-HTP

This may be an alternative or a problem-solving tool, when SSR imaging is negative. The sensitivity is higher for pancreatic NETs, as opposed to carcinoids, because there is no intracellular saturation from endogenous serotonin [58].

PET with ^{18}F FDG

^{18}F FDG is able to define prognosis in well-differentiated tumors given their low glucose substrate activity [29] and can, therefore, predict a response to PRRT [28]. It is the method of choice over ^{68}Ga -SSA-PET/CT in the identification and assessment of poorly differentiated G3 tumors, given their lower SSR expression [60].

Technique Limitations

Morphologic Imaging (table 3a)

Multidetector Computed Tomography

As assessment of hypervascular metastases, especially in the liver, is critically dependent upon the exact contrast enhancement phase and contrast medium dosage, additional difficulties, therefore, exist for reproducibility, which highlights the need for fully standardized guidelines and that these are implemented in the clinical routine [8]. Poorly demarcated large-volume liver disease is generally difficult to evaluate due to coalescence phenomena, which impede distinct

margin recognition, thereby limiting the possibility of response assessment using RECIST. Other limitations include the difficulty in clear identification of small lesions, especially small lymph nodes, peritoneal lesions and bone metastases. For small lymph nodes, even when they are depicted, the conventional size criteria are of very limited value to differ benign from metastatic lesions.

An important limitation with pure morphologic techniques such as MDCT is the risk of the underestimation of therapeutic response as defined by RECIST or SWOG response criteria. This reflects two issues, namely the latency period required for slow-growing tumors to shrink and the possibility of tumor necrosis, fibrosis or hemorrhage obscuring a decrease in tumor size [34]. A further limitation is the different response criteria that have been designated as a different volumetric 'demand' to define progression: a 40% volume increase for SWOG/WHO criteria versus a 73% volume increase for RECIST. This discrepancy may generate misperceptions in comparisons of 'accuracy' [61]. This limitation was recently outlined in the interpretation of the differential antiproliferative efficacy of lanreotide and octreotide in gastroenteropancreatic NETs. The discrepant results in these two different randomized trials which assessed the antiproliferative effects of lanreotide and octreotide should be regarded in view of the different definition of PFS used by each of the groups. The bidimensional nature of the WHO assessment employed in the octreotide study implied a lower tumor burden to define progression. This would have resulted in a shorter PFS and, therefore, a less substantial benefit for octreotide as opposed to lanreotide [62]. However, the potential impact of this variability should be reconsidered given the results of a recent retrospective analysis of PRRT data. In this study, both SWOG and RECIST criteria provided comparable results and predicted PFS and overall survival in a similar way [63].

Finally, radiation exposure and the use of iodinated contrast media, unsuitable for subjects with renal function impairment or those at risk for allergic reactions, represent other disadvantages.

Magnetic Resonance Imaging

Morphologic MRI shares with CT the same limitations inherent in anatomic imaging for the assessment of response to treatment [34]. Moreover, the costs, the limited availability, the extensive patient cooperation required and the lower familiarity of the clinicians are also problematic. Additionally, MRI is unsuitable for the study of

Table 3. Limitations of anatomic (a) and molecular imaging (b) techniques**a** Anatomic imaging

	MDCT	MRI	US techniques
Technical points	Radiation exposure	Cost	US techniques: operator dependency
	Use of iodinated contrast media may cause renal impairment and other adverse effects	Lack of wide availability	EUS: specialized expertise required, lack of wide availability
	Strict dependency on the exact contrast phase and dosage for comparability of especially hypervascular lesions	Long examination procedure	IOUS: operator dependency
Clinical points	Difficult (re)assessment of small-volume disease (e.g. small lymph nodes)	Extensive patient cooperation required	Abdominal US and CEUS: low sensitivity for GEP NETs, suboptimal assessment of pancreas and retroperitoneal lesions due to overlying abdominal structures
	Difficult (re)assessment of large-volume disease (coalescence)	Difficult (re)assessment of small-volume disease (e.g. small lymph nodes)	Difficult (re)assessment of large-volume disease, especially in the liver (poor demarcation, coalescence)
		Difficult assessment of small thoracic lesions	Thorax cannot be examined
	Difficulty in capturing modifications in slow-growing tumors	Difficult (re)assessment of large-volume disease (poor demarcation, coalescence)	
	Difficulty in defining response (e.g. RECIST) if necrosis/fibrosis/hemorrhage occurs without a marked decrease in tumor size	Difficulty in capturing modifications in slow-growing tumors	
		Difficulty in defining response (e.g. RECIST) if necrosis/fibrosis/hemorrhage occurs without a marked decrease in tumor size	

b Molecular imaging

	¹¹¹ In-pentetreotide	⁶⁸ Ga-PET	¹⁸ F-DOPA	¹¹ C-5-HTP	¹⁸ FDG
Technical points	Radiation exposure	Radiation exposure	Radiation exposure	Radiation exposure	Radiation exposure
	Low spatial resolution	Lack of full validation	Lack of full validation	Lack of full validation	
	Long procedure (2–4 days)	Lack of registration		Lack of registration	
Clinical points	Low sensitivity for insulinomas	Possible interference from cold analogues	Lack of therapeutic indications	Available only in specialized centers	Not validated for prognostication on large series
	Possible interference from cold analogues		Sensitivity seems inferior to receptor PET	Lack of therapeutic indications	

GEP = Gastroenteropancreatic.

small thoracic lesions because of the low signal-to-noise ratio in the lung, motion artifacts due to cardiac and respiratory activity and the lower spatial resolution as compared to CT [64].

US Techniques

The low sensitivity, the lack of reproducibility and operator dependency make abdominal US an inadequate tool for diagnosis and monitoring of therapy. For detection and characterization of liver lesions, CEUS is an excellent tool, but evaluation of the pancreas is restricted due to the presence of overlying bowel gas and other structures that impede optimal evaluation [65]. EUS and IOUS are similarly operator-dependent and require specialized expertise.

Molecular Imaging (table 3b)

SSR Imaging

The major limitation of conventional SRS with ^{111}In -pentetretotide is the low spatial resolution (approximately 1.5 cm) and, therefore, lower sensitivity compared to MRI and CT [37]. On a nonhybrid camera, lacking CT fusion, the procedure requires 2 and occasionally 3 days and, like any nuclear medicine procedure, has radiation exposure. The possibility of interference in the uptake by cold analogues and the low sensitivity for insulinomas due to their low SSR density, especially true for benign insulinomas, hamper SRS [66, 67].

Despite the orphan drug status of ^{68}Ga -DOTATOC, ^{68}Ga -DOTATATE and ^{68}Ga -DOTANOC, neither of the ^{68}Ga -DOTA-SSA are registered, which poses logistic difficulties. An additional major limitation of ^{68}Ga -SSA-PET/CT is the lack of reproducibility due to the lack of standardization as regards the preparation, the production procedure and examination protocols. Because of this variability and since tissue distribution of ^{68}Ga -DOTA-SSA is influenced by several other factors, PET measurements of SUV in tumor and normal tissues are not entirely reliable, although it has been demonstrated that SUV_{max} at preoperative ^{68}Ga -DOTANOC significantly correlated with the quantitative assessment of receptor density at immunohistochemistry for SSR2 and 5 in the surgical specimens [68].

PET/CT with ^{18}F -DOPA

Two limited-size studies report an inferior sensitivity of ^{18}F -DOPA compared to receptor PET [54, 55]. This technique thus requires validation in robust series [69]. Another limitation is the lack of a therapeutic counterpart.

PET/CT with ^{11}C -5-HTP

This modality requires an on-site cyclotron and is available only in a few specialized centers. The lack of full validation is a major limitation. In addition, there is no therapeutic application.

PET/CT with ^{18}F FDG

Despite some encouraging publications, the prognostic value in NETs has not been validated either in a large series or as a response to the available therapies [60].

The Future

Strategies to Advance Current Techniques (table 4)

Morphologic Imaging

Currently, lesion volume comparisons are based purely on monodimensional (RECIST) or rarely bidimensional (SWOG/WHO) assessments. Neither technique adequately delineates the actual course of the disease, given the modest volumetric changes in NETs and/or the possible simultaneous tissue modifications due to hemorrhage, fibrosis or tumor liquefaction. In this respect, attenuation measurement on CT, to assess the changes of Hounsfield units, may better define the post-therapeutic tissue variations. The Choi criteria incorporate attenuation measurements on CT and add a $\geq 15\%$ decrease of Hounsfield units to the 10% decrease in the longest lesion diameter as a parameter to indicate response [70]. These criteria, which were initially proposed for gastrointestinal stromal tumors, have also been tested for NETs [34] but require further validation.

A similar problem relates to the validation of examination protocols for comparing multiphasic imaging (CT and MRI) in order to ensure staging procedures are robust and reproducible. This is especially necessary for studies performed in different institutions which involve timing and duration of acquisition in relation to contrast medium injection, precise contrast medium dosage and contrast enhancement phase [71], and appearance of hypovascularization [72]. In order to obviate the integral problems inherent in a purely anatomical response evaluation, e.g. the variation in diameter, the integration of RECIST criteria with functional MRI parameters, such as arterial enhancement and necrosis, has been proposed. Following embolization of liver metastases, changes in each of these parameters have independently been associated with PFS [73].

SSR imaging has been demonstrated to timely predict the response to therapies such as SSA and PRRT [56,

Table 4. Opportunities for anatomic and molecular imaging techniques

	Advance in current techniques	Novel techniques and strategies
Anatomic imaging	Validation of Choi criteria for CT-based therapy monitoring	DWI techniques (ADC maps, pure diffusion parameters)
	Integration of molecular imaging in RECIST criteria (e.g. PERCIST) for therapy monitoring	DCE protocols for MRI, CT and US
	Integration of functional MRI parameters in RECIST criteria (e.g. vascularization, necrosis)	Validation of high-power magnetic fields (≥ 3 T)
	Validation of scanning protocols for multiphasic imaging (CT and MRI)	
Molecular imaging	^{68}Ga -SSA-PET validation (preferred peptide, peptide dose, preparation, quantification)	^{64}Cu -DOTA peptides
	^{18}F FDG validation	^{68}Ga -SSA-PET/MRI
	^{18}F -DOPA validation for therapy monitoring	Impact of ^{68}Ga -DOTA-SSA peptide mass
	Comparison of neuroendocrine metabolic and receptor PET tracers in large series	SSR antagonists
		GLP-1 receptor peptides
		Gastrin peptides
		Bombesin peptides
		Inhibitors of peripheral peptide degradations (e.g. phosphoramidon)
Merging biologic information to amplify accuracy	Validation of criteria arbitrarily merging biochemical, anatomic and molecular information	Scores merging imaging information with liquid biopsy (e.g. CTL, NET test)
		Scores merging imaging information with multianalyte assessment (NET test)
		Prognostic nomograms (CgA, MRI, CT, Ga-PET, etc.)

74]. It has been proposed that a further measure that could increase the accuracy of therapy monitoring is the integration of ^{68}Ga -SSA-PET/CT. This could be achieved in a similar way to the PERCIST criteria for FDG evaluation of responses to cancer therapy, where the SUV corrected for lean body mass, calculated in regions of interest of fixed diameter, is used to obtain a scale of response [75]. However, functional therapy monitoring with ^{68}Ga -DOTATOC by using tumor SUV changes during PRRT, as compared to baseline, has not yet produced convincing results [74, 76]. This could, at least partly, be related to differences in the administered amount of peptide between studies [77] and the fact that SUV does not seem to reflect SSR expression in tumors with a SUV >20 – 25 [78]. For therapy monitoring, diagnosis of progressive disease based on the appearance of new tumors could be more easily visualized with molecular imag-

ing, particularly lesions that generally are difficult to diagnose by CT, such as peritoneal lesions and bone metastases [79, 80].

Functional Imaging

In order to ensure acceptance by clinicians, ^{68}Ga -SSA-PET/CT needs to be developed as an efficient and reproducible molecular imaging procedure. There are several requirements that include: the choice of peptide, type of radiopharmaceutical preparation procedure and examination protocol in order to ensure reproducibility of the technique.

None of the three peptides currently in use (-TOC, -TATE and -NOC) demonstrates a clear diagnostic superiority over the others [81, 82]. Regarding preparation procedures, besides the European Pharmacopeia monograph on DOTATOC, the other ^{68}Ga -SSA preparations are syn-

thesized according to local, nonstandardized routines. As regards the reproducibility of the PET technique, despite some degree of uniformity offered by the EANM guidelines, current examination protocols vary in the acquisition time point in relation to tracer administration and in the amount of administered peptide. Also pertaining to this, there are large variations between centers on the view of the optimal preparation of the patients as regards the time interval between cold SSA injection and imaging. These factors, together with the inherent problems of PET measurements in tumors with high ^{68}Ga -SSA-uptake, as discussed previously [78], make SUV, the semiquantitative parameter to express uptake, less reliable. Moreover, SUV is intrinsically variable and may fluctuate among individual PET scanners and between centers unless these are cross-calibrated. Thus, the reproducibility of ^{68}Ga -SSA-PET/CT may vary with the type of preparation and its SSR subtype affinity profile, the examination time after tracer injection, scanning times (resulting in different phases of tumor uptake at the subsequent bed positions), the SSR saturation in tumors and nontumor tissues as a consequence of the injected amount of peptide and the relation to administration of cold SSA [83] and after splenectomy [84]. The use of tumor-to-normal-tissue ratios, such as tumor-to-liver and tumor-to-spleen, is a means to decrease the influence of these many factors that may reduce the accuracy of SUV measurements [74, 85]. Delineation of the patient's total tumor load, usually assisted by semiautomated software, has also been tested to calculate the 'total somatostatin receptor tumor volume' [78] or molecular tumor volume [86]. Particularly in larger centers, treating patients with PRRT, the increasing use of ^{68}Ga -SSA-PET/CT has rendered SRS obsolete, and the only remaining indication for SRS is to assess the patient's eligibility for PRRT. Therefore, an objective adaptation of the so-called 'Rotterdam scale' or 'Krenning scale' to ^{68}Ga -SSA-PET/CT needs to be developed to validate its predictive value.

Another important issue is a clinical validation of ^{18}F FDG uptake as a prognostic marker for NET aggression and as a tracer to monitor NET therapy response [27, 28]. Moreover, ^{18}F -DOPA should be validated and compared to ^{68}Ga -SSA-PET/CT in large series [31].

Novel Techniques and Strategies

Morphological Imaging

Diffusion-Weighted MRI

Diffusion-Weighted MRI (DWI) has been reported to be a sensitive modality to detect and characterize liver me-

tastases from NETs, with 71% sensitivity and 85–100% specificity. This is higher than the commonly used T2 fast spin echo or dynamic gadolinium-enhanced MRI [87]. DWI, therefore, is currently the most promising technique for investigating NETs, usually in combination with ^{68}Ga -SSA-PET/CT [88]. Interestingly, the newly introduced hybrid technique PET/MRI has not yet resulted in an increased sensitivity compared to the stand-alone techniques [89]. DWI for oncologic imaging is based on the restricted diffusion of water molecules in highly cellular tissue such as tumors and has shown potential for distinguishing exocrine and endocrine pancreatic tumors [90] and G1 from G2–G3 pancreatic neuroendocrine lesions by means of quantifying the tumor's apparent diffusion coefficient (ADC) in the images (ADC map) [91]. ADC has been shown to correlate with Ki67 [92]. To overcome the possible interference of tumor microcirculation in the measurements, an intravoxel incoherent motion model has been proposed to separate the true tissue diffusion; this results in a better characterization of pancreatic lesions [93]. Together with tumor size, the pure diffusion coefficient was able to differentiate G1 from G2 pancreatic NETs [94].

Dynamic Contrast-Enhanced Imaging

Dynamic contrast-enhanced (DCE) imaging is applied to MRI, CT and US [31, 34, 95]. In contrast to PET/CT, it is not a whole-body technique, and the examination generally needs to be focused to include a limited axial field of view. The technique requires substantial validation in consideration of the large intraindividual variability (20% for DCE MRI) and the lack of linear correlation between gadolinium concentrations in the tissue and the resulting signal intensity [31, 96]. It has been recently demonstrated that perfusion parameters at DCE MRI have a definite pattern in malignant liver metastases. The flow-related parameters, such as the arterial plasma flow and the arterial flow fraction, are both correlated with the mean SUV derived from ^{68}Ga -DOTATATE-PET (negatively) and ^{18}F FDG-PET (positively). This suggests that functional and molecular techniques evaluate different aspects of liver function and may offer complementary information [97].

DCE MRI parameters have also been used to monitor the response to PRRT [98]. Specific parameters related to perfusion and tissue exchange were spatially correlated with the heterogeneous uptake of ^{111}In -pentetreotide in a pancreatic NET model in rats [99]. Regions with high exchange-related parameters demonstrated high tracer uptake, and these parameters were better predictors of uptake as compared to parameters associated with the total

amount of contrast. Clinical confirmation of these observations would have important therapeutic and prognostic implications [99].

Functional Imaging

⁶⁴Cu Labeling

SSA labeled with ⁶⁴Cu is of interest due to the excellent image quality compared to conventional scintigraphy and the possibility of imaging at a later time compared to ⁶⁸Ga-SSA, thus matching more closely the kinetics of receptor uptake, namely 3 and 24 h after injection, due to the 12.5-hour half-life. The latter allows for easy distribution to other diagnostic centers. Drawbacks are the need for a cyclotron for its production and a higher radiation dose to the patient as compared to ⁶⁸Ga-SSA (⁶⁸Ga $t_{1/2}$ 68 min). Direct comparisons with ⁶⁸Ga-SSA-PET/CT are warranted [24].

Novel SSA Antagonists

Besides radiolabeled SSA, the workhorse of nuclear-medicine NET imaging for 2 decades, alternative radiopharmaceuticals with an increased diagnostic accuracy [100] have been identified and developed. In this respect, the use of SSR antagonists represents a highly promising strategy [101]. The lack of internalization and the recognition of increased binding sites is an inversion of the current paradigm of agonist binding and is, therefore, of great interest to explore. Paradoxically, antagonists result in a higher and longer retention in tumors and better imaging results [102]. In vitro, the ¹⁷⁷Lu-labeled compound DOTA-BASS binds to more receptor sites than the agonist DOTATATE, while, in vivo, the same peptide labeled with ¹¹¹In demonstrated a higher tumor uptake than ¹¹¹In-pentetreotide. This implies a higher sensitivity compared to conventional scintigraphy and may translate, using the therapeutic counterpart, into a greater treatment benefit [102, 103].

GLP-1 Receptor Peptides

The development of novel receptor peptides that can identify a particular tumor or one with a specific secretory product needs to be investigated. A number of peptides have been tested in preclinical and clinical trials. Among these, GLP-1 receptor peptides, like ¹¹¹In-exendin-4 for the localization of occult insulinomas, are the most advanced for clinical application [104]. ¹¹¹In-exendin-4 addresses the general paucity of SSRs in insulinoma. GLP-R and SSR imaging, therefore, demonstrate the biologically mutable aspect of insulinomas, which may be GLP-R positive and SSR negative or vice versa, a reflec-

tion of their malignant phenotype [105]. In this respect, ⁶⁸Ga-exendin-4 has been recently tested for PET/CT imaging in clinical practice [106, 107].

Others

Other receptor peptides potentially of use in NET imaging include GRP receptor ligands, such as bombesin agonists and antagonists labeled with ^{99m}Tc or with ⁶⁸Ga, and gastrin/cholecystokinin analogs, such as ¹¹¹In-labeled minigastrin. The low plasma stability and high kidney retention, however, classically limited the diffusion of these peptides [100]. Nevertheless, newer, more stable molecules and the coadministration of specific enzyme inhibitors, such as the neutral endopeptidase inhibitor phosphoramidon, can be utilized to increase the bioavailability of these compounds [108]. Alternative strategies include the use of ⁸⁹Zr-labeled bevacizumab to evaluate NETs of different origins treated with everolimus. A decrease in the SUV during treatment suggested that this technique could be an early predictor of the efficacy of antiangiogenesis treatments [109].

Integration of Biological Information to Amplify Accuracy

Biological Indices

In order to advance NET diagnosis and better predict prognosis and optimize therapies, there is a need to integrate the biological information of tumor pathophysiology with anatomic and molecular diagnostic strategies. Thus, the relationship between the intrinsic variability of individual NET cells (EC, β , ECL, D, Clara, etc.) that comprise the different tumor types and imaging strategies requires investigation. This should include a delineation of histopathological indices, high-throughput molecular analyses, receptor subtyping and characterization as well as the determination of metabolic parameters that define function and proliferation.

Nomograms

It is clear that monoanalyte-derived information can never be as effective as the product of multianalyte parameters. Thus, an image alone is, by definition, limited by the lack of additional, relevant parameters that can be integrated into an amplifiable diagnostic quotient. Inclusion of such additional material, in a mathematical probability index, or in a matrix or via a nomogram, has proved of considerable added value in other disciplines [110].

Fig. 3. Time line of imaging development in NETs. ^{131}I -MIBG = ^{131}I -metaiodobenzylguanidine; ^{11}C -HTP = ^{11}C -hydroxytryptophan.

Recently, various studies have explored the combination of the information deriving from imaging with clinical and biologic data, in order to obtain predictive algorithms that are able to confer a higher accuracy to diagnostic techniques. As an example, a combination of morphologic information, such as tumor size >4 cm and presence of lymph nodes when combined with biological information, such as the tumor grade, has been utilized in a model, deriving from the multiple logistic regression of a retrospective series, that is able to predict the preoperative risk of lymph node metastasis in nonfunctioning pancreatic NETs [111].

A more detailed nomogram was constructed to determine prognosis of small intestine NETs. This utilized 15 clinical and biological variables, such as age, symptoms, 5-HIAA, CgA, tumor size, invasion, metastasis, histology, Ki67 index and adopted therapy. The resulting score was able to identify significant differences in survival, thus demonstrating that a multilevel parallel assessment of different forms of tumor-/patient-relevant information may be an appropriate tool that can strengthen both diagnostic and prognostic accuracy [110].

Recently, a mathematical model incorporating proliferation, infiltration, metabolism and mass effect has been proposed to estimate the tumor growth in pancreatic NETs. This includes integration of the theoretical equations with the observations derived from dual-phase con-

trast-enhanced CT and FDG-PET. However, in the absence of tumors' inherent biological parameters, the model only reflected a current situation and could not predict future progression [112].

To amplify information provided by NET imaging techniques, the integration of tumor features and blood-based biomarkers into prognostic nomograms may be useful. An informative source of information would be the integration of tumor data, such as circulating tumor cells and relevant genes, detected through mRNA measurement or circulating autoantibodies, with imaging [113]. In particular, circulating genomic data obtained from blood (tumor transcript profile or signature) at the time of imaging could be combined with morphologic or functional tumor characteristics and, thus, allow for the development of a personalized predictive assessment of tumor status before, during and after treatment [3].

Coda

Diagnostic imaging has substantially advanced in the past 40 years (fig. 3). This development has been facilitated by the collaboration between medicine professionals and industrial partners. It is evident that progress occurs through team-based science, and future multidisciplinary teams in our hospitals need not only include

medicine professionals but also experts on genomics, laboratory medicine and epidemiology. Given the complexity of the carcinogenic process, the intrinsic heterogeneity of cancer and tumor microenvironment, it is unlikely that any single diagnostic test will be effective. Rather, NET diagnosis will be a process utilizing a variety of methods including genomics-epigenomics-proteomics on biosamples such as blood, urine and tumor tissue in combination with anatomical and molecular imaging (hybrid imaging) for localization, delineation and staging of the disease, as the basis for optimal selection of therapy.

Future advances in NET diagnosis need to consider two realities. Firstly, a short-term accelerated strategy to focus upon validation of the present techniques or sequences of techniques. The second is a long-term strategy, to develop a more comprehensive multilevel integration of biologic and genomic information to provide added value to the imaging techniques. This will aim at facilitating recognition of the complete status of an individual tumor. Thus, a fusion product of molecular and genomic information with tumor imaging is likely to be the quintessence of future NET diagnosis and define the progress from darkness to light.

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