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Abstract

Imaging of gastroenteropancreatic neuroendocrine tumors can be broadly divided into anatomic and functional techniques. Anatomic imaging determines the local extent of the primary lesion, providing crucial information required for surgical planning. Functional imaging, not only determines the extent of metastatic disease spread, but also provides important information with regard to the biologic behavior of the tumor, allowing clinicians to decide on the most appropriate forms of treatment. We review the current literature on this subject, with emphasis on the strengths of each imaging modality.

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Key words: Magnetic resonance imaging; Neuroendocrine tumor; Positron emission tomography; Somatostatin receptor scintigraphy

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INTRODUCTION

Neuroendocrine tumors (NETs) are a rare and heterogeneous group of neoplasms, which as the name suggests, are derived from cells of the neuroendocrine system. It was Lubarsch et al. [1] in 1888, a German pathologist at the University of Munich, who is generally credited with the first report of a carcinoid tumor. He gave the classical microscopic description of multiple ileal carcinoids in two patients, termed “little carcinomata”, which he thought originated in the intestinal crypts of Lieberkuhn.

Later in 1907, Ciacco M C coined the term “enterochromaffin” to describe the cells that were thought to give rise to the tumor, and this was further expanded by Feyrter et al. [2], who proposed the concept of the diffuse neuroendocrine system in an attempt to unify tumors in diverse sites that had similar histological features.

The term neuroendocrine is derived from the similarity of such cells to neural cells in the expression of certain proteins, such as synaptophysin, neuron-specific enolase and chromogranin A. Currently, the following criteria proposed by Langley [3] are generally accepted as defining neuroendocrine cells: (1) The production of a neurotransmitter, neuromodulator or neuropeptide hormone; (2) The presence of dense-core secretory granules from which the hormones are released by exocytosis in response to an external stimulus; and (3) The absence of axons and synapses.

DIAGNOSIS OF NEUROENDOCRINE TUMORS

The morphologic appearance of well-differentiated NETs
is fairly typical, demonstrating an organoid-type pattern under light microscopy, and diagnosis can be fairly confidently made on the basis of such morphology. In cases of poorly differentiated tumors or neuroendocrine origin or variant morphology, electron microscopy or immunohistochemical assessments might be necessary[4,5].

Several commonly used immunohistochemical markers include synaptophysin, chromogranin, vasoactive monoamine transporter 2, serotonin and substance P[6]. Chromogranin appears to be the most consistent general marker, and has been found to have high sensitivity and specificity in diagnosing NETs[7]. In addition, circulating levels of chromogranin A have been found to correlate with tumor volume and are related to disease extent, and could potentially play a role in disease monitoring and prognostication[8,9].

CLASSIFICATION AND STAGING OF NEUROENDOCRINE TUMORS

Historically, the diverse and widespread nature of disease presentation meant that a large number of descriptions have been used for NETs in different body regions. Also, certain descriptive terms have been used loosely with different connotations between physicians, surgeons and pathologists, leading to further confusion and miscommunication. In response, attempts have been made to organize and categorize the tumors that comprise the neuroendocrine disease spectrum. In 2000, the World Health Organization (WHO) published a classification for NETs of the gastroenteropancreatic system that categorized tumors into 3 broad categories[10]: (1) Well-differentiated neuroendocrine tumor (benign or uncertain malignant potential); (2) Well-differentiated neuroendocrine carcinoma (low grade malignancy); and (3) Poorly differentiated neuroendocrine carcinoma (high grade malignancy). The criteria used for differentiating the various grades include tumor size, angioinvasion, proliferative activity, histological differentiation, presence of metastasis/local invasion, association with certain syndromes, and hormonal/functional activity.

In an attempt to clarify terminology, the term “carcinoid” was reserved to describe well-differentiated NETs, and the term “malignant carcinoid” was used to describe well-differentiated neuroendocrine carcinomas.

Several publications have supported the clinical effectiveness of the WHO criteria in management decision support (Table 1)[11-14], but there was a need for improved prognostication assessment of NETs.

In response, the European Neuroendocrine Tumor Society has attempted to address the staging of NETs. Their staging system addressed 2 issues; the cell characteristics/proliferation capacity of the tumor, and an adapted tumor node metastasis (TNM) staging system[15-17].

The TNM staging system was sub-divided into specific areas such as the stomach, duodenum/proximal jejunum, lower jejunum/ileum, and pancreas, and follows conventional grading criteria assessing for tumor size/invasion, nodal and distant spread.

With regard to cellular grading, three tumor grade categories were identified. Grade 1 tumors show a low proliferative index (Ki67 < 2% or < 2 mitoses per HPF), Grade II tumors show a moderate proliferative index (Ki67 3%-20% or 2-20 mitoses per HPF), and Grade III tumors show a high proliferative index (Ki67 > 20% or > 20 mitoses per HPF). In general, Grade 1 and 2 tumors should refer to well-differentiated NETs while Grade 3 tumors indicate poorly differentiated neuroendocrine carcinomas.

Publications have supported the utility of this TNM classification system for prognostication stratification (Table 2)[18], but further validation is required.

ANATOMIC IMAGING OF NEUROENDOCRINE TUMORS

Anatomic imaging of NETs still plays a crucial role in the diagnosis and management of this condition, largely due to its ability to provide anatomical information for surgical planning. The widespread availability of ultrasound (US) and computed tomography (CT), and in most large centers, magnetic resonance imaging (MRI), has led to a number of publications on the imaging detection of NET. Due to the relative paucity of this condition, most of the published data describing the efficacy of each
modality, and consequently studies directly comparing between modalities, suffer from small sample sizes with wide variability in results. Nevertheless, for gastroenteropancreatic (GEP) NETs, it is generally agreed upon that CT and MRI are superior to US, both in terms of lesion detection, and characterization.

### Ultrasound

The use of transabdominal ultrasound (TAUS) in GEP NETs is largely confined to the solid viscera. This is due to the fact that sound waves are heavily attenuated by air, and US is therefore not usually suitable for assessment of lesions within the gastrointestinal tract or mesentery. The use of US in tumor diagnosis and staging is further limited by inter-operator variability. Nevertheless, newer techniques, such as contrast enhanced US (CEUS) and endoscopic US (EUS), have found a greater role for US in the management of GEP NETs.

The use of TAUS for assessment of pancreatic lesions is limited, especially in the body and tail region, which are commonly obscured by air and ingested material in the overlying stomach. Therefore, the patient should ideally have fasted for several hours prior to scanning. Using the stomach and proximal duodenum as an acoustic win-

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**Table 2a Tumor node metastasis staging (gastric, duodenum, ampulla, jejunum, ileum, pancreas)**

| TNM staging | Gastric | Duodenum/ampulla/proximal jejunum | Pancreas | Lower jejunum/ileum |
|-------------|--------|-----------------------------------|---------|--------------------|-----------------|
| Tx          | Primary tumor cannot be assessed | Primary tumor cannot be assessed | Primary tumor cannot be assessed | Primary tumor cannot be assessed |
| T0          | No evidence of primary tumor     | No evidence of primary tumor     | No evidence of primary tumor     | No evidence of primary tumor     |
| Tis         | In situ tumor/dysplasia (>0.5 mm)| -                                | -                                | -                                |
| T1          | Tumor invades lamina propria or submucosa and <1 cm | Tumor invades lamina propria or submucosa and <=1 cm | Tumor limited to pancreas and size <2 cm | Tumor invades musculis propri or size 2-4 cm |
| T2          | Tumor invades muscularis propria or subserosa or >1 cm | Tumor invades muscularis propri or >1 cm | Tumor limited to pancreas and size 2-4 cm | Tumor invades subserosa |
| T3          | Tumor penetrates serosa          | Tumor invades pancreas or retroperitoneum | Tumor limited to pancreas and size 4 cm or invading duodenum or bile duct | Tumor invades peritoneum/other organs for multiple tumors |
| T4          | Tumors invade adjacent structures (for any T, add M for multiple tumors) | Tumor invades peritoneum or other structures (for any T, add M for multiple tumors) | Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall or large vessels (celiac or superior mesenteric artery) | Tumor invades peritoneum/other organs (for any T, add M for multiple tumors) |
| Nx          | Regional lymph nodes cannot be assessed | Regional lymph nodes cannot be assessed | Regional lymph nodes cannot be assessed | Regional lymph nodes cannot be assessed |
| N0          | No regional lymph node metastasis | No regional lymph node metastasis | No regional lymph node metastasis | No regional lymph node metastasis |
| N1          | Regional lymph node metastasis | Regional lymph node metastasis | Regional lymph node metastasis | Regional lymph node metastasis |
| Mx          | Distant metastasis cannot be assessed | Distant metastasis cannot be assessed | Distant metastasis cannot be assessed | Distant metastasis cannot be assessed |
| M0          | No distant metastasis | No distant metastasis | No distant metastasis | No distant metastasis |
| M1          | Distant metastasis | Distant metastasis | Distant metastasis | Distant metastasis |

**Table 2b Tumor node metastasis Staging (appendix, colon, rectum)**

| Appendix | Colon/rectum |
|----------|--------------|
| Tx       | Primary Tumor cannot be assessed |
| T0       | No evidence of primary tumor |
| T1       | Tumor invades lamina propria or submucosa and <=1 cm |
| T2       | Tumor invades submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesosappendix and <=2 cm |
| T3       | Tumor >2 cm and/or invasion (more than 3 mm) of the serosa/mesosappendix |
| T4       | Tumors invade peritoneum/other organs |
| Nx       | Regional lymph nodes cannot be assessed |
| N0       | No regional lymph node metastasis |
| N1       | Regional lymph node metastasis |
| Mx       | Distant metastasis cannot be assessed |
| M0       | No distant metastasis |
| M1       | Distant metastasis |
Table 2c: ESMO tumor node metastasis clinical classification of neuroendocrine tumors

| Disease stage | T    | N     | M     |
|---------------|------|-------|-------|
| Gastric, duodenum, ampulla, jejenum, ileum, pancreas |       |       |       |
| Stage I      | T1   | N0    | M0    |
| Stage IIa    | T2   | N0    | M0    |
| Stage IIb    | T3   | N0    | M0    |
| Stage IIIa   | T4   | N0    | M0    |
| Stage IIIb   | Any T| N1    | M0    |
| Stage IV     | Any T| Any N| M1    |
| Appendix     |      |       |       |
| Stage I      | T1   | N0    | M0    |
| Stage IIa    | T2   | N0    | M0    |
| Stage IIb    | T3   | N0    | M0    |
| Stage IIIa   | T4   | N0    | M0    |
| Stage IIIb   | Any T| N1    | M0    |
| Stage IV     | Any T| Any N| M1    |
| Colon/rectum |      |       |       |
| Stage Ia     | T1a  | N0    | M0    |
| Stage Ib     | T1b  | N0    | M0    |
| Stage IIa    | T2   | N0    | M0    |
| Stage IIb    | T3   | N0    | M0    |
| Stage IIIa   | T4   | N0    | M0    |
| Stage IIIb   | Any T| N1    | M0    |
| Stage IV     | Any T| Any N| M1    |

dow by drinking water is recommended[29]. Characteristic features of pancreatic NETs on US would be a homogenously hypoechoic mass that may sometimes have a hyperechoic halo. Use of CEUS shows promise but requires validation. Detection rate of US for pancreatic NET varies widely and ranges from 0%-66%[20].

EUS is a more invasive method of imaging assessment. Its advantage over TAUS lies in the fact that the US probe is positioned much closer to the organ of interest. This allows the use of higher frequency probes 7.5-12 MHz which provide better spatial resolution in the order of millimeters. Rosch et al[31] reported a sensitivity of 82% and a specificity of 95% for EUS in localizing pancreatic NET lesions. In a similar study by McAuley et al[20] on insulinomas, for lesions smaller than 2 cm in diameter, EUS carried a sensitivity of 80%-90%, leading the authors to recommend EUS as a screening tool for patients with a known diagnosis of multiple endocrine neoplasia (MEN) type 1. While previously considered to represent the gold standard of assessment of NETs, preoperative imaging by CT and MRI has largely superseded intraoperative US (IOUS). This is partly because IOUS entails a longer operating time, and carries with it the potential risk of iatrogenic injury (e.g. to the splenic vein) during the course of examination.

**CT**

Significant improvements in the spatial and temporal resolution of CT have been made over the past decade, with the advent of multidetector row CT (MDCT). This has allowed for multiphasic contrast enhanced CT (CECT) while achieving spatial resolutions in the order of millimeters. The use of biphasic or triphasic CECT is generally considered a prerequisite for detection and characterization of NETs, both for primary disease involving the pancreas, as well as for liver metastases (Figure 1). The reason for this is that the majority of NET lesions show avid early enhancement. CT is regarded as a first-line imaging modality for detection and staging of NETs.

A recommended protocol for imaging of pancreatic NETs would require the patient to be adequately fasted. Ingestion of water just before the CT scan would act as a negative contrast for visualization of peripancreatic tumors. An unenhanced scan can initially be performed to look for calcifications, which occur in around 20% of cases, and differentiate this from pancreatic adenocarcinomas, which calcify in only approximately 2% of cases[28]. Thin collimation allows for depiction of submillimeter lesions, and this is usually performed at 1.25 to 2.0 mm section thickness[23]. Multiphase reconstructions may also help improve lesion assessment.

Typically, intravenous administration of iodinated contrast at a rate of 3-5 mL/s is required to provide an adequate bolus. Most MDCT scanners are equipped with automated bolus tracking capabilities, hence allowing for patient-specific adjustments of scan delay times following bolus injection of contrast. On average, arterial phase imaging is performed at 20-25 s following initiation of contrast injection, while the portal venous phase is timed at approximately 50 s. The pancreatic parenchymal phase, which is the time at which the pancreas enhances maximally, is usually at 35-40 s.

The typical pancreatic NET lesion is isodense on the non-contrast scan but shows homogeneous avid arterial enhancement. Vascular encasement and biliary obstruction are considered rare. Atypical lesions include those that are hypovascular (or hypoenhancing), hyperdense on non-contrast scan, cystic (Figure 2) or calcified[22,28]. Non-functioning lesions tend to be larger, and present with mass effect such as biliary dilatation. They may, therefore, appear as heterogeneous lesions with central necrosis or cystic degeneration. Functioning tumors are usually small, with around 50% of lesions measuring less than 1.3 cm in diameter, and therefore, do not cause deformation of the contour of the gland. The main differential for pancreatic NETs would be metastases from clear cell type renal cell carcinoma, both of which may be present in patients with von Hippel Lindau's disease.

CT has the advantage of a wider field of view than US. It is, therefore, suited for detection of nodal and metastatic disease. In the presence of a NET originating from the bowel, the high contrast to noise ratio between the primary lesion and mesenteric fat allows for excellent depiction of the extent of mesenteric retraction (Figure 3). The secondary lesions, most notably liver metastases, tend to show a similar imaging pattern as the primary lesion itself. Esophageal hyperenhancement and small bowel mural thickening are concomitant findings associated with gastrinomas and best depicted on CT.

In terms of lesion detection, sensitivity of detection with CT increases proportionately with lesion size. In gastric NETs, Binstock et al[26] showed that those lesions that were larger than 1 cm in diameter and presented with focal wall thickening were detected with increased fre-
quency. Similarly, for the small bowel lesions, CT was able to detect around half of the lesions when the size of the mesenteric masses exceeded 1.5 cm\(^2\). Interestingly, it is not uncommon to find that the sizes of the metastatic lesions far exceed the size of the primary tumor (Figure 4).

Improvements in CT technology over time, probably also due to the use of multiphasic CECT, have led to a concomitant increase in lesion detection of pancreatic NETs. For example, a retrospective study of cases over 13 years by Gouya et al\(^{28}\) in 2003, showed lesion sensitivity of 94.4% with the use of dual phase thin section CT compared to 28.6% with the use of single slice section CT technology.

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Similarity, for metastatic disease to the liver, which can be the most common imaging finding in GI NETs, multiphasic imaging is recommended, with the hepatic arterial phase being best for lesion detection\(^{29}\). On standard radiography and CT, bone metastases frequently demonstrate either an osteosclerotic or a mixed osteolytic-osteosclerotic pattern\(^{30}\).

Magnetic resonance imaging
MRI is considered superior to CT for lesion assessment in the solid visceral organs. In a comparison study between MRI and CT as well as angiography for detection of metastatic lesions, MRI was shown to be superior\(^{31}\).

As with CT, multiphasic CE MRI is recommended, with fat-suppressed CE T1-weighted (T1W) imaging providing the best accuracy, with an area under the receiver-operating curve (AUROC) of 0.98\(^{32}\). This has been corroborated by a more recent study by Herwick et al\(^{33}\).

The advantages of MRI over CT are the lack of ionizing radiation and the use of gadolinium chelate contrast agents, which have a better safety profile in terms of allergic reactions and nephrotoxicity, although the latter point is slightly mitigated by the concerns of nephrogenic systemic fibrosis. Nonetheless, MRI provides added information about the lesions, such as T1 relaxivity and T2 dephasing.

Typically, NET lesions show T2 hyperintensity and T1 hypointensity (Figure 5). In the study by Owen et al\(^{34}\), 14 out of 29 (48.3%) lesions demonstrated this finding, while only one out of 29 (3.4%) showed a reversal of signal, that is, T1 hyperintensity and T2 hypointensity. The study by Semelka et al\(^{35}\) showed a positive predictive value of 96%.
for MRI in pancreatic NETs. Gastrinomas tend to show ring or peripheral enhancement while most other subtypes of NETs demonstrated a diffuse pattern of enhancement.

For GI NETs, MRI is able to detect around two-thirds of lesions, with fat-suppressed T1W imaging yielding maximal results. Similarly, hepatic metastases are well depicted on MRI, and MRI is often used to further characterize lesions that are equivocal on CT. Bader et al. showed this finding in 75% of cases. Interestingly, 15% of cases showed increased enhancement only in the arterial phase. Furthermore, some of the metastases may display T2 hyperintensity approaching that of hemangiomas. Nevertheless, T2WI and hepatic arterial phase T1WI fat-suppressed imaging have been shown to be most sensitive.

Advances in diffusion weighted imaging (DWI) have led to its widespread clinical use in abdominal imaging. Vossen et al. showed that there was a statistically significant difference in apparent diffusion coefficient (ADC) values between hemangiomas and NET metastases (as well as other hypervascular liver lesions), with an AUROC of 0.91. An added advantage of using DWI is its ability to reflect lesion changes in treatment response. In the study by Liapi et al., ADC values rose concomitantly with response to transarterial chemoembolization (TACE), in tandem with decreased enhancement of the treated lesions. For the primary lesions, DWI may allow for preoperative localization of tumors in the pancreas, especially those which do not demonstrate the typical hypervascular pattern.

FUNCTIONAL IMAGING OF NEUROENDOCRINE TUMORS

The basis of functional imaging lies with the targeted detection of specific cell targets or receptors, allowing precise localization of lesions. In the context of diagnostic imaging, the concentration of receptor molecules in target tissues may be hard to differentiate from background nonspecific binding. As such, molecular imaging techniques have often been confined to nuclear-based modalities such as positron emission tomography (PET) or single photon emission CT (SPECT), which are able to generate images with micromolar to picomolar concentrations of imaging probes.
The Delphi consensus with regard to the diagnostic imaging of NETs, has acknowledged that functional imaging in the form of somatostatin receptor scintigraphy (SRS) plays a central role in the diagnosis of NETs[43], and we will explore this and various other functional imaging modalities and techniques in relation to their clinical utility in the diagnosis of NETs. Our discussion will focus largely on the gastroenteropancreatic system, but general principles are likely applicable to NETs in other parts of the body.

**Somatostatin receptor scintigraphy**
Somatostatin receptors are widely distributed in the human nervous system and tissues in the body, including the adrenals, kidneys, pancreas and prostate[46]. Currently, 5 subtypes of somatostatin receptors have been identified in humans (SSRT1, SSRT2, SSRT3, SSRT4, SSRT5), with SSRT2 further classified into subtypes 2A and 2B[47].

Of particular interest, somatostatin receptor expression has been found in a large number of tumors, of which NETs are the archetypical class, and this forms the basis for the molecular imaging of NETs. The half-life of somatostatin itself is too short (<2 min) for use in either diagnosis or therapy. As a result, synthetic somatostatin analogues with sufficiently long half-lives have been developed for use in diagnostic imaging or therapeutics.

The first commercially available somatostatin analogue was Octreotide (Sandostatin, Novartis Pharmaceutical Corp), with an approximate half-life of 2 h, and a radio labelled analogue of octreotide, Octreoscan® [111In-DTPA-Octreotide, D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr[ol]], was successfully used to visualize somatostatin receptor positive tumors by gamma camera scintigraphy in the early 1990s[48-50].

Normal physiological uptake is seen in the thyroid, spleen, liver and pituitary due to receptor binding of the peptides, while tracer uptake in the kidneys is predominantly secondary to reabsorption of filtered peptides, and bowel uptake is presumably secondary to hepatobiliary clearance (Figures 6 and 7).

Gamma-based SRS (Octreoscan®) has proved to be a safe, sensitive imaging agent in the detection of GEP NETs, with an overall sensitivity of approximately 80%-90% in patients with gastrointestinal neuroendocrine neoplasms[47,54]. However, limitations include false negative results in organs with significant physiological uptake (e.g. liver) where background uptake may mask lesions, and small volume diseases that may be below the intrinsic spatial resolution of gamma imaging. Additionally, false positives can occur with a variety of lesions, such as the thyroid gland, accessory spleens, granulomatous or inflammatory tissue, and benign or malignant breast lesions[55]. Other types of neoplasms that demonstrate somatostatin receptor expression include meningiomas and lymphomas.

Nonetheless, SRS is considered the “gold standard” in the diagnosis, staging and follow-up of patients with NETs (Figure 8).

Newer generation somatostatin analogues have since been developed, allowing radiolabeling with positron emitting tracers. Together with the development and adoption of hybrid PET/CT modalities, this potentially addresses several limitations faced with first generation SRS, largely related to the poorer spatial resolution of gamma-based probes and the issue of precise anatomical localization (Figures 9 and 10).

PET-based SRS has shown high sensitivities, specificities and accuracies in the evaluation of NETs. Initial evaluations using PET-based SRS were encouraging. Hoffmann et al[56] found higher tumor to non-tumor contrast ratios with significantly higher detection ratios for PET-based SRS, and Kowalski et al[57] also concluded that PET-based SRS was able to detect more lesions and was superior in detecting smaller lesions.

A larger prospective study by Gabriel et al[59] evaluating the diagnostic value of 68Ga-DOTATOC PET in 84 patients with known or suspected NETs demonstrated a sensitivity of 97%, specificity of 92% and an overall accuracy of 96%, showing significantly higher diagnostic efficacy as compared with SPECT imaging using gamma-based SRS and normal diagnostic CT. In addition, PET-based SRS detected more tumor sites in the liver, nodes and bone as compared with the other modalities, and provided further clinically relevant information in 14% of patients compared with gamma-based scintigraphy and 21% as compared with CT.

This was substantiated by Putzer et al[60], who evaluated 51 patients with histologically proven NETs with 68Ga-DOTATOC PET/CT. Reported sensitivity and specificity were 97% and 92%, respectively, higher than CT or bone scan, and detected bone metastasis in patients at a significantly higher rate. This is particularly important as osseous metastasis has a negative prognostic implication on clinical outcomes.

**Tan EH et al. Imaging of gastroenteropancreatic NETs**

**Figure 6** Gallium 68 DOTATATE positron emission tomography from the skull vertex to mid-thigh. The coronal maximum intensity projection image demonstrates physiological areas of tracer uptake in the pituitary (black arrowhead), kidneys (black arrows), liver and spleen (curved arrows).
Furthermore, the increased diagnostic accuracy of PET-based SRS has been shown in publications to impact on actual clinical management. Ambrosini et al. [60] evaluated the clinical impact of 68Ga-DOTANOC PET/CT imaging in 90 patients with histologically proven NETs. In the subgroup of patients with concordant PET and CT findings (n = 47), PET resulted in a modification of therapeutic management in 36.2% of patients. In the subgroup of patients with discordant PET and CT findings (n = 42), PET resulted in stage modification in 28.6% of patients and a change in management in 76.2% of patients. Overall, PET imaging affected either staging or therapy in 55.5% of patients imaged, with the most frequent management impact being initiation or continuance of peptide receptor radionuclide therapy, initiation or continuance of somatostatin analogue treatment, or referral for surgery. The author also reported

Figure 7  Indium 111 Octreotide Planar whole-body images. A: Indium 111 Octreotide 24-h delayed anterior and posterior planar whole body images in a patient with prior resected pancreatic neuroendocrine carcinoma. Several abnormal tracer foci (white arrows) are seen in the peri-hepatic region, suspicious for somatostatin receptor expressing lesions. These were later confirmed as neuroendocrine nodal metastasis in the peri-hepatic and peri-gastric nodes; B: Indium 111 Octreotide 24-h delayed anterior and posterior planar whole body images in a patient with histologically confirmed neuroendocrine carcinoma of the pancreatic body. Increased tracer focus in the region of the pancreas (curved white arrow) corresponds to the primary pancreatic lesion, while multiple abnormal foci of uptake in the liver (white arrows) are in keeping with hepatic metastasis.

Figure 8  Patient with prior history of neuroendocrine carcinoma in the pancreatic tail, status post partial pancreatectomy and splenectomy. A: Gallium 68 DOTATATE positron emission tomography/computed tomography (PET/CT). Axial CT and fused PET/CT images of the abdomen shows a mass in the left upper abdomen demonstrating significant DOTATATE tracer avidity (white arrow). Considerations included tumor recurrence or splenunculus; B: Technetium 99m Sulfur Colloid scintigraphy. Anterior and posterior planar spot views of the upper abdomen demonstrates a focus of uptake (black arrows) in the left upper abdomen, corresponding to the area of uptake seen on the previous Gallium 68 DOTATATE scan, confirming the mass to be a splenunculus.
that PET prevented unnecessary surgery in 6 patients, and excluded 2 patients with peptide receptor radionuclide treatment who did not show significant somatostatin analogue avidity.

With regard to post-therapy response assessment of NETs following peptide receptor radionuclide therapy, findings are controversial. Gabriel et al \cite{61} evaluated 46 patients with advanced NETs who underwent peptide receptor radionuclide therapy. 68Ga-DOTATOC PET (dedicated PET) and conventional CT was performed pre- and post-therapy for all patients. RECIST criteria were used to evaluate therapy response, with a reported 30% response rate, 48% stable disease and 22% progressive disease. Concordant findings were noted in 70% of cases. In the 30% discrepant group (n = 14), PET-based SRS outperformed CT in 10 patients, was able to detect lesions not seen on CT in 5 patients and accurately determined disease response in 5 patients. In contrast, CT was able to detect small pulmonary lesions in 1 patient not seen on PET, and in the remaining 3 patients, PET-based SRS showed decreased tracer uptake in the lesions, but these were due to tumor dedifferentiation rather than therapy response, while CT clearly showed tumor size and extent of progression.

The author concluded that PET-based SRS showed no advantages over conventional imaging in response assessment, but several limitations in the study have to be noted. Firstly, the study utilized a dedicated PET scanner, while the majority of newer installations are hybrid PET/CT scanners, and the intrinsic limitations of dedicated PET imaging is accounted. Indeed, based on the 4 discrepant findings reported in the study, if a hybrid PET/CT scanner was utilized, it is expected that such discrepancies would not exist. Secondly, the emergence of non-somatostatin analogue avid lesions on post-therapy assessment scans is of clinical use, as it indicates dedifferentiation of tumor, suggesting the need for alternative treatment from peptide receptor radionuclide therapy or somatostatin analogues (Figures 9 and 10).

Overall, PET-based SRS has been routinely found to demonstrate high diagnostic sensitivity, specificity and accuracy, with positive clinical impact during pre-therapy staging. The use of SRS for post-therapy assessment is more indeterminate, and further evaluation needs to be carried out.

**F18-fluorodeoxyglucose PET/CT**

Fluorodeoxyglucose (FDG) PET imaging is a molecular imaging technique that addresses the glucose metabolism of tissue. As a rule of thumb, malignant tumors tend to demonstrate significantly higher levels of glucose metabolism as compared with normal physiological tissue, and this has proven true across a wide range of tumor types\cite{63}.

The molecular basis of increased glucose metabolism...
in tumor cells is complex, and there appears a multitude of factors controlling aerobic glycolysis in tumors \[64\]. However, 2 major factors have been implicated with increased FDG tumor uptake. Firstly, the overexpression of glucose transporters and activity in tumor cells (predominantly GLUT-1, 3 and 5) which actively drive glucose into the cells, and secondly, the overexpression of hexokinase enzymes (predominantly hexokinase-2) that increase glucose metabolism \[65,66\].

The use of FDG PET in NETs is currently controversial. There are limited sensitivities overall, but there is emerging evidence that the presence of increased glucose metabolism in tumors highlights an increased propensity for invasion and metastasis, and overall poorer prognosis. This correlates with mathematically-based telogenic models and empiric data reviewed by Gillies \textit{et al.} \[67\], where such increased glucose metabolism confers an “evolutionary advantage” in cancer cells over normal parenchymal tissue.

An early study performed by Adams \textit{et al.} \[68\] found that FDG PET only demonstrated increased glucose uptake in less differentiated tumors with high proliferative activity. Another small study performed by Pasquali \textit{et al.} \[69\] evaluated the clinical use of FDG PET against conventional gamma-based SRS and CT, and again found that FDG PET was able to detect NETs characterized by rapid growth or aggressive behavior. Garin \textit{et al.} \[70\] performed a prospective study evaluating the clinical outcomes of 38 patients with metastatic NETs. FDG PET, SRS and conventional CT were performed for these patients, and patients were tracked to determine progression-free survival and overall survival. Overall 2 year survival and progression-free survival was 73\% and 45\%, respectively, and it was found that most patients with FDG PET positive lesions had early progressive disease (14/15 for FDG PET positive as compared with 2/23 for FDG PET negative). Furthermore, when only patients with low-grade tumors were considered, FDG PET was able to predict those with early progression. Progression-free survival was 87\% ± 7\% and 75\% ± 10\% at 1 and 2 years, respectively, for FDG PET negative lesions, as compared with 7\% ± 6\% and 0\% at 1 and 2 years, respectively, for FDG PET positive patients. Overall, the relative risk of early progression with FDG PET positive lesions was 10.7 (95\% CI: 2.8-40.6).

In terms of survival, FDG PET negative patients fared better than patients with FDG avid lesions. Overall survival was 95\% ± 5\% at both 1 and 2 years, respectively, for FDG PET negative patients, vs 72\% ± 12\% and 42\% ± 13\% at 1 and 2 years, respectively, for 18F-FDG PET positive patients.

Overall, the use of FDG PET appears promising in disease prognostication, possibly influencing aggressiveness of management. In addition, dual tracer imaging using both FDG and SRS PET might possibly be used in post-therapy assessment following peptide receptor radionuclide therapy to evaluate for tumor dedifferentiation or the “flip-flop” phenomenon \[71\] (Figure 11).
The APUD Concept by Everson Pearse describes the ability of neuroendocrine type cells to take up and decarboxylate amino acid precursors, and there have been various efforts to evaluate the utility of radiolabeled amine precursors to image NETs. Examples of such precursors include hydroxytryptophan, hydroxyephedrine, dopamine and dihydroxyphenylalanine (DOPA). The radiolabeled DOPA analogues are transported into NETs via the sodium independent system L, and the activity of amino acid decarboxylase in the cells is important for intracellular retention of the metabolized radiolabeled DOPA analogue. Becherer et al. in the evaluation of 23 patients with histologically proven NETs concluded that 18F-DOPA PET performed better that gamma-based SRS in visualizing lesions, with the highest sensitivity in visualizing skeletal and mediastinal lesions. Reported sensitivities were 81.3% for the liver, 90.9% for the skeleton and 100% for the mediastinum and lymph nodes.

Koopmans et al. evaluated 53 patients in a prospective single-center diagnostic accuracy study using 18F-DOPA PET, conventional CT and SRS without any CT correlation, and reported that 18F-DOPA PET detected more lesions, more positive regions and more lesions per region as compared with the other modalities. Reported sensitivities at the patient, region and lesion levels were 100%, 95% and 96%, respectively.

Kauhanen et al. evaluated 82 patients with suspected/known NETs using 18F-DOPA PET, comparing the diagnostic accuracy with histological findings and clinical follow-up. 32 patients were for primary diagnosis and staging, while 61 patients were for restaging. Overall accuracy for gastrointestinal NETs was approximately 89%.

Overall, based on a meta-analysis by Jager et al., the radiolabeled DOPA analogues have reported sensitivities in the range of 65%-96% for the detection of individual lesions, with most of the values in the upper half of this range.

The advantages of DOPA PET over conventional anatomic imaging or gamma-based SRS are fairly conclusive, but the role in comparison with PET-based SRS techniques is still uncertain. Accuracies for PET-based
Table 3 Summary comparison of the various imaging modalities

| Advantages | Disadvantages | Utility |
|------------|--------------|---------|
| Ultrasound | Widely available modality, dynamic visualization of lesions, no ionizing radiation | Limited to solid organ systems, inter-operator variability | Possible use as a screening tool for assessing the liver and pancreatic head First line imaging modality |
| CT         | Widely available modality, wide field of view, allowing evaluation of nodal disease and metastasis, good sensitivity | Not as widely available as compared with CT or ultrasound, more specialized diagnostic imaging expertise in interpretation, lower specificity in characterizing neuroendocrine lesions as compared with functional imaging modalities | Local staging of disease, including vascular involvement, use in pediatric age group in which ionizing radiation is of greater concern |
| MRI       | Superior to CT for assessment in solid organs, no ionizing radiation, gadolinium contrast agent safety profile better than CT agents in terms of allergic reaction and nephrotoxicity, ability to further characterize lesions using different sequencing | Ionizing radiation; not as widely available as CT or ultrasound, requiring nuclear imaging capabilities; more specialized diagnostic imaging expertise in interpretation | Gold standard in the evaluation of neuroendocrine tumors |
| SRS       | Good sensitivity and specificity, able to accurately characterize lesions; single modality staging; allows for dosimetric evaluation of suitability for peptide receptor radionuclide therapy; proven impact on clinical management | | |
| Fluorodeoxyglucose PET | Possible use in disease prognostication and management stratification, possible use in post treatment assessment to evaluate for tumor dedifferentiation | Generally poor sensitivity for neuroendocrine tumors, ionizing radiation | Not routinely performed for neuroendocrine tumor assessment, possible utility in prognostication and post therapy assessment |
| Diiodohydroxyphenylalanine PET | Good sensitivities in the evaluation of neuroendocrine tumors, shows promise especially in assessments of insulinomas | Requires more specialized nuclear facilities (e.g. gaseous F18) for synthesis of the radioisotope, PET based SRS has generally similar or better accuracies in the detection and staging of neuroendocrine tumors, ionizing radiation | Possible clinical utility in the evaluation of insulinomas |

CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; SRS: Somatostatin receptor scintigraphy.

FUNCTIONAL IMAGING OF PANCREATIC NEUROENDOCRINE TUMORS

Pancreatic endocrine tumors comprise approximately 2%-10% of all pancreatic tumors\(^86\)\(^,\)\(^87\), and are named after the predominant hormone that they secrete.

Insulinomas are the most common, accounting for approximately 60% of pancreatic NETs. They are tumors arising from pancreatic B-cells and are frequently solitary and largely benign. Typically, only 10% of insulinomas are multiple, 10% malignant, and 10% are associated with the Multiple Endocrine Neoplasm (MEN) type 1 syndrome\(^88\). Gastrinomas are the second most common tumors, accounting for approximately 20% of such tumors. Other rarer types include glucagonomas, somatostatinomas, vasoactive intestinal peptide secreting tumors (VIPomas), adrenocorticotropic secreting tumors (ACTHomas), GRFomas, calcitonin-producing tumors and parathyroid hormone-related peptide tumors.

Such tumors can be broadly classified as functional or non-functional, and although earlier studies estimated non-functional tumors to account for 18%-66% of tumors\(^81\), later large studies have classified 60%-80% of pancreatic NETs as non-functional\(^82\)\(^,\)\(^83\).

In approaching functional or molecular imaging of pancreatic neuroendocrine or islet-cell tumors, it is prudent to do so based on 2 separate groups: Insulinomas and non-insulinoma pancreatic NETs.

With regard to insulinomas, the role of SRS is uncertain, as there is generally poor sensitivity in the detection of such tumors. The reasons for this are multifactorial. Firstly, a significant percentage of insulinomas do not express significant densities of somatostatin receptors, especially subtypes 2 and 5. In addition, somatostatin receptors are not significantly expressed in non-malignant insulinomas further limiting SRS sensitivity\(^84\). However, malignant insulinomas are known to overexpress somatostatin receptors, and SRS has potential imaging roles in such tumors for prognostication and staging\(^85\).

In contrast, gamma-based SRS has reported sensitivity and specificity for non-insulinoma pancreatic NETs of approximately 80%-90%\(^86\)\(^,\)\(^87\), and is indicated for use in pre-therapy localization and staging, especially when demonstration of extra-hepatic metastatic lesions is required.
Several reports have established the promising utility of PET-based SRS for imaging non-insulinoma pancreatic NETs. The use of PET-based SRS is expected to have improved resolutive capabilities as compared with conventional gamma-based SRS, in keeping with findings from gastrointestinal carcinoid imaging, but further validation is needed.

The utility of FDG PET in the evaluation of pancreatic NETs is indeterminate. FDG PET has generally poor sensitivities in the detection of such tumors (approximately 50%)[5], but may have a role in prognostication as it allows the identification of NETs characterized by aggressive growth or behavior[2-9].

DOPA PET appears to show promise in the evaluation of pancreatic NETs. Koopmans et al[6] in the evaluation of 23 patients with pancreatic islet cell tumors reported a sensitivity of 89% using 18F-DOPA PET, as compared with 78% and 87% for gamma-based SRS and conventional CT, respectively.

In the same study, 5-hydroxytryptophan (5-HTP) was also used as a delivery ligand in the targeted imaging of NETs. 5-HTP is the direct precursor for the serotonin pathway, and thus, is potentially of use in all neuroendocrine type tumors.[6] In relation to pancreatic islet cell tumors, the study reported sensitivities of 100% for 11C-5-HTP in the detection of pancreatic NETs (Table 3).

CONCLUSION

The discussions on the various imaging modalities used in the diagnostic imaging of NETs highlight several of the modalities and various key points, but this is not a comprehensive review. This is partly due to the extensive and complex nature or NETs, and partly due to the explosive growth and developments in medical imaging. In summary, an understanding of the historical and molecular underpinnings of NETs, and the intrinsic uses and limitations of each diagnostic imaging modality, are essential for the physician involved in the management of this complex disease.

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