# Imaging in Pancreatic Neuroendocrine Tumors

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# Abstract

# **Keywords**

- computed tomography
- ► imaging
- magnetic resonance imaging
- neuroendocrine tumors
- pancreas
- pancreatic malignancies

# Introduction

Pancreatic neuroendocrine tumors (NET) are rare neoplasms with a reported incidence of 0.3-0.4/100,000 and account for approximately 3 to 5% of all pancreatic malignancies.<sup>1-3</sup> These tumors have a better prognosis compared with pancreatic adenocarcinomas, with an overall 5-year survival rate of 42%. For resectable tumors, the 5-year survival is around 55% while for unresectable tumors, it decreases to approximately 15%.4,5 These tumors may occur sporadically or in association with syndromes such as von Hippel-Lindau (vHL) syndrome, neurofibromatosis type I (NF1), multiple endocrine neoplasia type I (MEN-I), and tuberous sclerosis (TS).6,7 They arise from the islet cells of the pancreas and are similar in histology to carcinoid tumors of the gastrointestinal tract; thus, these lesions are together grouped under gastroenteropancreatic neuroendocrine tumors (GEP NETs).8 All these are epithelial neoplasms with predominant neuroendocrine differentiation.9

Imaging characterization of these lesions depends on whether the tumor is functional or nonfunctional

The challenge in imaging of functional tumors is to locate the source as these tend to be small. On the other hand, nonfunctioning tumors are large in size; thus, imaging is needed to differentiate these from other neoplasms. Another important aim of imaging is to look at

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Pancreatic neuroendocrine tumors (NETs) form a discrete subgroup of pancreatic neoplasms. They are rarer than pancreatic adenocarcinomas but need to be differentiated from other pancreatic tumors and pathologies as they carry a better prognosis. Imaging plays a central role in detecting, characterizing, and staging of pancreatic NETs as they tend to have typical radiological features. A lot of advancements have taken place in the field of imaging and theranostics which have revolutionized their detection and management. In this article we shall review the various imaging techniques available to the radiologist, salient imaging features of different types of pancreatic NETs, staging and grading systems, as well as a brief overview of their management.

dissemination and to assess resectability of these tumors. With the advent of newer nuclear medicine techniques and advancements in computed tomography (CT) and magnetic resonance imaging (MRI), it has become possible to provide accurate assessment of primary lesions as well as its spread which helps in optimizing treatment protocols. With the advent of perfusion imaging, diffusion-weighted imaging, intravoxel-incoherent motion and texture analysis, it may be possible to predict the biological behavior of these lesions.<sup>10-13</sup>

Aims of imaging in neuroendocrine tumors:

- 1. Detecting the presence of a hyperenhancing mass.
- 2. Accurate localization of the lesion.
- 3. Suggesting the possible diagnosis and characterize it.
- 4. Assessing resectability and distant spread.
- 5. Predicting whether the tumor will respond to therapy.
- 6. Early detection of residual disease or recurrence.
- 7. Assessing other tumors which may have a syndromic association.

# **Imaging Techniques**

#### Ultrasound

Ultrasound (US) is the first imaging investigation in a patient presenting with abdominal pain.

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It may serve to detect a lesion in such symptomatic patients or rarely may detect larger lesions incidentally. However, its utility is limited as visualization of smaller focal lesions of pancreas may be obscured by bowel gas.<sup>14,15</sup> The reported sensitivity of US for detection of GP-NETs is reported to be around 13 to 37%.<sup>16</sup> If visualized on US, they usually appear as hypoechoic masses with a hyperechoic halo.<sup>15</sup> US may be more useful in visualizing and sampling metastatic liver lesions.<sup>17</sup> Once a lesion is detected on US, CT or MRI is the next step for proper characterization and staging of these lesions.

## **Computed Tomography**

Due to its easy availability, high spatial resolution, rapid acquisition and low cost, computed tomography (CT) has long been the workhorse of pancreatic imaging. Newer techniques such as dual-energy imaging, perfusion analysis have further added to the robustness of CT in picking up small NETs. A pancreatic protocol CT usually involves acquisition of upper abdomen in the pancreatic phase (at 35–40 s after contrast injection) followed by portal venous phase acquisition (at 60–70 s) of the entire abdomen and pelvis. Neutral oral contrast may be administered to distend small bowel loops. A noncontrast scan is not needed.

The pancreatic phase corresponds to the late arterial phase and may be acquired in dual energy mode so as to enable generation of virtual noncontrast dataset as well as for increased conspicuity of hyperenhancing lesions at low keV images. Usually, 80 to 120 mL of iodinated contrast is injected intravenously at a flow rate of 4 to 5 mL/s followed by saline chase. All acquisition is volumetric with thin collimation. Arterial phase also helps to assess resectability by demonstrating tumor involvement of the celiac and superior mesenteric arteries and their branches.

The reported sensitivity and specificity of CT for detection of NETs is at approximately 73% and 96%, respectively (**- Fig. 1**).<sup>14</sup> The sensitivity is affected by the phase of acquisition, ranging from 83 to 100% in the arterial phase to 11 to 76% for portal venous phase<sup>18-21</sup>; thus, the need of early phase. In a small study of 16 patients, evaluation of iodine material decomposition images and low kV monochromatic images yielded a significantly higher sensitivity of 95.7% for detection of insulinomas compared with a sensitivity of 68.8% for routine dual phase images (**- Fig. 2**).<sup>22</sup>

#### Magnetic Resonance Imaging

With its multitude of sequences, magnetic resonance imaging (MRI) offers better lesion to parenchyma contrast than CT.<sup>10</sup> It allows for lesion visualization even without administration of contrast (hence can be used in patients with renal derangement and in patients with contrast allergy) and can be safely used in young patients as there is no ionizing radiation involved. The disadvantages of MRI include higher cost, limited availability, and longer imaging times; thus, it is predominantly used as a problem-solving modality.<sup>10</sup> The recommended MRI protocol is provided in **~ Table 1**.



**Fig. 1** (**A**–**B**) Arterial ([**A**] axial, [**B**] coronal) and venous ([**C**] axial, [**D**] coronal) phase images show presence of an arterial enhancing mass in the head of pancreas (arrow) with a central focus of calcification. Multiple arterial enhancing lesions are also seen in segments 6 and 8 of liver (arrowheads). Here, the lesion and metastases are well seen in both the phases.



**Fig. 2** Utility of dual energy CT in imaging pancreatic neuroendocrine tumors. Iodine overlay map (**A**) and virtual noncontrast image (**B**) showing a solid cystic mass in the pancreatic head with definite iodine uptake in the solid component in the iodine overlay images (arrow in **A**) in a patient with nonfunctional neuroendocrine tumor.

Sequence	Matrix size	Slice thickness	TR	TE	Utility
Axial T2-FS	200 × 200	5 mm	2,132	80	NETs are hyperintense on T2
Coronal T2	200 × 200	5 mm	332	80	
Axial BTFE/true FISP	200 × 200	5 mm	2.7	1.33	Fast sequence, also helps delineate relation- ship with vessels
Axial dual FFE / T1 in and opposed phase	188 × 121	5 mm	89	2.3/4.6	For characterization of T1 signal and to detect intracellular fat
Thick slab heavily T2W MRCP	320 × 256	40 mm	8,000	800	For assessment of pancreatic and biliary ducts
3D RESTORE heavily T2W MRCP					For assessment of pancreatic and biliary ducts
Axial DWI (b-values 0 and 500–800 s/mm²)	125 × 100	5 mm	4,365	64	Improves sensitivity of detection of primary and metastatic lesions
Dynamic pre and post Gd T1 mDIXON/VIBE: pancreatic, venous and delayed phases	200 × 200	3 mm	5.9	1.80/4.0	Arterial and venous phases are essential for detection and characterization of neuroen- docrine tumors
Coronal post Gd T1 mDIXON	200 × 200	3 mm	5.9	1.80/4.0	

 Table 1
 Suggested MRI protocol for imaging pancreatic NETs

Abbreviations: BTFE, balanced turbo field-echo; DWI, diffusion-weighted imaging; FISP, fast imaging with steady state precession; FFE, fast field echo; MRCP, magnetic resonance cholangiopancreatography; NET, neuroendocrine tumors; VIBE, volume interpolated body examination.

The reported sensitivity and specificity of MRI for detection of neuroendocrine tumors has been reported to be 93% and 88%, respectively (>Fig. 3). In addition to the routine T1, T2, and arterial phase images, diffusion-weighted imaging (DWI) has been shown to improve lesion detection, differentiating intrapancreatic accessory spleen from NET as well as differentiating from other pancreatic lesions.<sup>23-25</sup> Apart from lesion detection, MRI has also been shown to be better than CT in detection of liver metastasis and evaluating tumor gra de.<sup>10,12,26</sup> Ill-defined margins, larger size, necrosis, predominant solid component, arterial hypoenhancement, pancreatic duct dilatation, presence of metastases, and diffusion restriction were more common in grade 3 than in grade 1 or 2 NETs.<sup>27,28</sup> In addition different DWI-based texture analysis parameters including correlation, contrast, inverse difference moment, maximum intensity, and entropy have been shown to differ between different grades of pancreatic NETs.<sup>27</sup>

# Nuclear Medicine

Traditionally somatostatin receptor scintigraphy has been used for detection of NETs. This is done by using octreotide, which is an analogue of somatostatin and binds to somatostatin receptors 2 and 5 (out of the 5 types of somatostatin receptors).<sup>29</sup> To enable its detection, octreotide is labeled with indium-111 (In-111), which emits low energy gamma photons which can be imaged using planar and single photon emission CT (SPECT) gamma cameras. Imaging is done at 4 hours and 24 hours after administration of In-111-labeled octreotide. For better localization of the tumor, a SPECT may be combined with a CT.<sup>30</sup> The reported sensitivity of In-111 scintigraphy for detection of pancreatic NETs is reported to be around 70 to 90%. Its sensitivity is significantly reduced for subcentimeter lesions and for insulinomas which express the type 3 somatostatin receptors.<sup>30,31</sup>



Fig. 3 (A-F) – shows a T1 hypointense (A, B - in and opposed phase), T2 heterogeneously hyperintense mass (C) in the head of pancreas showing no intracellular fat (A). The mass shows intense diffusion restriction (D) with heterogeneous arterial phase enhancement (E) sand washout on venous phase images (F). Histopathology confirmed the diagnosis of neuroendocrine tumor.

PET-CT offers improved spatial resolution with lower radiation dose than SPECT and hence is now the preferred imaging technique for detection of NETs. PET imaging requires labeling of agents with photon emitters like gallium (Ga)-68 and fluorine (F)-18.32 Somatostatin analogues developed for PET-CT include DOTA-tyrosine-3-octreotide (DOTA-TOC) with affinity for somatostatin receptor 2 and DOTA-Nal-octreotide (DOTA-NOC), which binds to the receptor subtypes 2, 3, and 5 (Fig. 4). These two are labeled with Ga-68 for use.<sup>31</sup> Fluorodeoxyglucose (18-FDG) is nonspecific and taken up by metabolically active tumors, and thus can be used for imaging poorly differentiated NETs.<sup>30</sup> Hence a combined approach can be used for both detection and characterization of NETs. Poorly-differentiated NETs are negative on DOTA-NOC PET but show uptake on FDG PET. The sensitivity and specificity of PET-CT has been reported to be 93% and 95%, respectively.<sup>33</sup> Another approach being used is targeting of metabolic pathways, by tagging amino acid precursors such as dihydroxyphenylalanine (DOPA) with F-18 and hydroxytryptophan (5-HTP) with carbon-11 (C-11).<sup>34</sup> Efforts are also on to use the same concept for targeting these tumors using the approach of theranostics using peptide receptor radionuclide therapy (PRRT). Diagnostic SPECT/PET imaging agents (In-111/Ga-68 DOTATOC/-TATE) are tagged to therapeutic isotopes such as yttrium-90 (Y-90) and lutetium-177 (Lu-177) and used to deliver targeted high-dose radiotherapy.<sup>10</sup>

# **Contrast-Enhanced Ultrasound**

Intravenous ultrasound contrast agents are increasingly being used for diverse diseases. They are blood pool agents without a tissue phase and hence can give information about blood flow. Although approved by the United States Food and Drug Administration for cardiac imaging and evaluation of focal liver lesions, they are increasingly being



**Fig. 4** Role of nuclear medicine in imaging patients with MEN-1 syndrome. (**A**) A mass in the pancreatic tail (arrow) showing uptake in 68Ga-NOTA-exendin-4 PET/CT suggesting presence of insulinoma. In the same patients, Ga-68 DOTANOC PET/CT showed other lesions in the right inferior parathyroid (**B**) as well as in the pancreatic uncinate (**C**) which were resected. Final histopathology confirmed presence of parathyroid adenoma and gastrinoma in the uncinate process of pancreas.



**Fig. 5** Contrast-enhanced ultrasound (CEUS) image (**A**) showing intense uptake of contrast agent in the pancreatic head mass in early phase (asterisk). Corresponding gray scale image (**B**) shows a heterogeneous mass in the head of pancreas of mixed echogenicity which on resection was confirmed to be a non-functioning neuroendocrine tumor.

used for imaging other parts of the body due to their relative safety. Early studies have shown promising results with reported sensitivity of 87–89% for contrast-enhanced ultrasound (CEUS) compared with 24% for US alone in detection and localization of insulinomas (**~Fig. 5**).<sup>35</sup>Endoscopic Ultrasound

Sometimes, a lesion may be visualized on cross-sectional imaging but may not show typical features of NET. At times, the lesion may be too small or doubtful, producing just subtle contour bulge or slightly different attenuation/ signal intensity. These are the scenarios where endoscopic ultrasound (EUS) may come to the rescue. It has been reported to have a mean detection rate of around 90% and has the additional advantage of providing the opportunity to sample the lesion in the same sitting.<sup>36</sup> The main disadvantage of EUS and EUS-guided fine needle aspiration cytology (FNAC) is that the technique is invasive and hence is associated with morbidity in ~ 1% cases.<sup>37</sup>

# **Imaging Findings**

For the purpose of discussion of imaging findings of NETs, they can broadly be divided into functional and nonfunctional tumors. Functional tumors usually present early on account of the symptoms they cause while nonfunctional tumors may stay clinically occult and reach large size before manifesting clinically. They usually present with pressure symptoms or may even be incidentally detected. Around 85% of pancreatic NETs are functional in nature.<sup>38</sup>

#### Functional Pancreatic Neuroendocrine Tumors

Functional pancreatic NETs manifest with systemic symptoms and are usually less than 2 cm at the time of imaging.<sup>16,20,39</sup> Here the challenge is to detect the location of the tumor and map its spread. The most common functional pancreatic NETs are insulinomas and gastrinomas.<sup>10</sup> Glucagonomas, somatostatinomas, and vasoactive intestinal peptide-secreting tumors (VIPomas) complete the list of functional pancreatic NETs.

# **General Imaging Characteristics**

Functional NETs tend to be uniformly hypervascular and well-defined with intense arterial phase enhancement with washout on portal venous phase images.<sup>20,39</sup> Though the sensitivity of arterial phase images is higher (~83–88%) than venous phase images (~11–76%), it is important to evaluate both these phases carefully since the lesions may be seen on either one of the phases.<sup>10,18,20</sup>

Features like cystic change, heterogeneity, calcifications, and necrosis are generally seen in larger tumors but may uncommonly occur even in smaller tumors.<sup>40</sup> Cystic tumors with a thin peripheral rim are seen in around 5 to 10% of cases.<sup>20</sup>

Though most functional neuroendocrine tumors share these imaging characteristics, it is imperative to discuss them individually to comprehensively understand their clinicoradiological presentation.

## Insulinomas

The classical presentation of insulinomas is Whipple triad which consists of symptoms of hypoglycemia which are relieved after glucose ingestion and documented low glucose levels in blood. Insulinomas tend to be small, solitary, intrapancreatic lesions which are usually benign (in 90% cases); 97% of insulinomas are intrapancreatic, ~90% are solitary, and 40% are less than 1 cm in size.<sup>10</sup> Tumor size of more than 3 cm should raise the suspicion of malignancy while multiplicity suggests syndromic association such as multiple endocrine neoplasia type 1 (MEN-1).<sup>39,41,42</sup> Less than 10% of insulinomas are associated with MEN-1 syndrome.43 Insulinomas express somatostatin receptor type 3 and hence sensitivity of octreotide scan is limited (~50%) (octreotide binds to receptors 2 and 5).<sup>29,31,44</sup> CT and MRI are often more useful with good sensitivity (**Fig. 6**).<sup>10</sup> However, the sensitivity of newer PET-CT techniques has been reported to be approximately 84 to 97%.45,46 A newer PET-CT metabolite, glucagon-like peptide-1 receptor 68Ga-NOTA-exendin-4 PET/CT has been shown to have high sensitivity (~99%) for detection of insulinomas<sup>46,47</sup> (**~Fig. 4**).



**Fig. 6** (**A–D**) Presence of a T2 heterogeneously hyperintense mass in the head of pancreas showing intense diffusion restriction (**A**). The lesion shows arterial phase enhancement (**C**) with washout in the venous phase images (**D**) consistent with a neuroendocrine tumor. Final histopathology confirmed the mass to be an insulinoma.

It is important to not only locally stage the tumor but also to look identify nodal and liver metastasis.<sup>39</sup> The sensitivity and specificity of Ga-68 DOTANOC PET/CT is reported to be around 97% and 100% for detection of metastases.<sup>48</sup> Though invasive techniques such as arterial stimulation and venous sampling, and transhepatic portal venous sampling have been conventionally used to improve localization, they are seldom used in current era owing to high sensitivity of various imaging modalities. Intraoperative US remains the gold standard for delimiting the lesion<sup>30,42,49</sup> and is especially important when localized resections are planned.

#### Gastrinomas

Clinically, gastrinomas present with abdominal pain, secretory diarrhea, and hypercalcemia. Biochemically there is increased basal acid output, maximal acid output and serum gastrin levels. In contrast to insulinomas, gastrinomas are not exclusively intrapancreatic. More than a third of these tumors are located in extrapancreatic locations including the duodenum and peripancreatic lymph nodes<sup>10</sup>; 90% of gastrinomas are located in the gastrinoma triangle, bound by the junction of the cystic duct with the common bile duct superiorly; junction of the second and



Fig. 7 (A, B) Presence of marked gastric rugal fold thickening predominantly in the fundus and proximal body of stomach (asterisk). A mass lesion was seen in the gastrohepatic location (arrow in A) which on histopathology was consistent with a gastrinoma.



**Fig. 8** Axial arterial (**A**) and venous phase (**B**) images showing a large heterogeneous mass in the pancreatic bed with chunky foci of calcification (arrows) which on histopathology was proven to be a poorly differentiated neuroendocrine tumor.

third part of duodenum inferolaterally, and the pancreatic neck medially. Less commonly, lesions may occur in the stomach and jejunum.<sup>20,39</sup> Presence of gastric rugal thickening in association with hypervascular lesion in gastrinoma triangle suggests the diagnosis of gastrinoma (**-Fig. 7**). Pancreatic gastrinomas usually occur in the head and tend to be larger lesions typically around 3 to 4 cm in size.<sup>50</sup> In contradistinction, duodenal lesions are typically subcentimetric and multiple.<sup>50</sup> Hence, CT and MRI are typically better in detecting pancreatic lesions. Overall, EUS plays an important role in diagnosing gastrinomas and allows sampling of the lesion and or lymph nodes.<sup>20</sup> Detection and staging may also be aided by octreotide scan or PET-CT as they express a high concentration of somatostatin receptors.

A higher percentage of gastrinomas (~50–60%) are malignant at the time of diagnosis and that necessitates watchful inspection of locoregional nodes and the liver.<sup>20</sup> About 15 to 35% of gastrinomas are associated with MEN-1 syndrome and thus gastrinomas are the commonest NET in this syndrome.<sup>43</sup>

## Glucagonomas

After insulinomas and gastrinomas, glucagonomas are the third most common functional pancreatic NETs. The diagnosis is usually clinical with a diagnostic triad of hyperglycemia, necrolytic migratory erythema, and venous thrombosis. Serum glucagon levels more than 1,000 pg/mL are diagnostic.<sup>43</sup> On cross-sectional imaging, these tend to be large tumors and are easily visible on imaging. Nuclear medicine scans are also helpful in localizing metastasis, if any.

## **Other Functional Pancreatic NETs**

These are rare include VIPomas and somatostatinomas. VIPoma presents with Verner–Morrison syndrome, which is characterized by the clinical triad of watery diarrhea, hypokalemia, and achlorhydria. Serum levels of VIP more than 200 pg/mL are diagnostic. Somatostatin causes a decrease in the secretion of pancreatic enzymes, insulin, and cholecystokinin by the pancreas. Its oversecretion, thus, is clinically characterized by diarrhea, steatorrhea,

diabetes, and gall stones. Most somatostatinomas are malignant and may have metastases at presentation. Fasting serum somatostatin levels above 100 pg/mL are diagnostic.

#### Nonfunctioning Pancreatic Neuroendocrine Tumors

Nonfunctioning pancreatic NETs present with symptoms secondary to mass effect, including abdominal pain, jaundice, and weight loss. They tend to be larger in size at presentation.<sup>20,40</sup> Up to one-third of nonfunctional pancreatic NETs may be found incidentally.<sup>51</sup> The term nonfunctioning is a misnomer because these tumors might secrete hormones such as pancreatic polypeptide, neurotensin, neuron-specific enolase, chromogranin A,  $\alpha$  subunit of human chorionic gonadotropin, etc.. However, there is no clinical manifestation of these secretions.<sup>10</sup> The larger size is associated with greater heterogeneity with areas of cystic change, necrosis, and foci of calcification (Fig. 1). Some of these tumors may be predominantly cystic and may mimic solid pseudopapillary tumors.<sup>40</sup> In addition, they are more likely to be metastatic at presentation (60-80%) with lymph nodes and liver being common sites of metastasis.<sup>16,20</sup> The tumor is more likely to be malignant if it contains foci of calcification (Fig. 8).16 Neuroendocrine tumors may be associated with ductal dilation due to obstruction as well as can spread within the distended duct.<sup>16,20</sup> About one-third of the nonfunctioning NETs may be associated with intravascular invasion manifesting as venous tumor thrombus.<sup>52</sup> Multiple nonfunctional NETs may occur in MEN-1 and VHL syndrome or may occur sporadically ( - Figs. 1, 9, 10).20

# **Grading of Pancreatic Endocrine Tumors**

Grading of pancreatic neuroendocrine tumors is done using the ENETS/WHO grading system 2019.<sup>53</sup>

Well-differentiated NETs are divided into 3 categories:

- Grade 1 (low grade): mitotic rate < 2 per 10 high-power fields and Ki67 rate < 3%.
- Grade 2 (intermediate grade): mitotic rate 2 to 20 per 10 high-power fields or Ki67 rate 3 to 20%.
- Grade 3 (high grade): mitotic rate > 20 per 10 high-power fields or Ki67 rate > 20%.



Fig. 9 Coronal CT images showing an enhancing nonfunctioning pancreatic neuroendocrine tumor (arrow in A) and concomitant pheochromocytoma (asterisk in B) in a patient of von Hippel–Lindau syndrome.



**Fig. 10** (**A-F**) Two synchronous pancreatic neuroendocrine tumors in the uncinate (arrow) and tail of pancreas (arrowhead). The lesions were T1 hypointense (**A**, **B**), T2 hyperintense (**C**, **D**) with early enhancement (**E**, **F**). No syndromic association could be established.

Poorly differentiated NETs are termed neuroendocrine carcinomas and are high-grade lesions which can be small-cell type or large-cell type. Poorly differentiated NETs portend a poorer prognosis for the patient and have a higher propensity for lymph nodal and/ or liver metastasis. They are dedifferentiated tumors which

ryce	Juge	involvement
Stage	grouping	
I	T1N0M0	Tumor size <2 cm, confined to the pancreas. No nodal/metastatic involvement
II	T2N0M0	Tumor size ≥2 cm, <4 cm, confined to the pancreas. No nodal/metastatic involvement
	T3N0M0	Tumor size >4 cm, confined to the pancreas OR tumor involving the duodenum/ common bile duct (CBD). No nodal/ metastatic involvement
III	T4N0M0	Tumor involving adjacent organs including stomach/spleen/colon/adrenal OR tumor involving celiac axis/superior mesenteric artery. No nodal/metastatic deposit
	Any T, N1M0	Irrespective of tumor size and local invasion, involvement of regional lymph nodes. No metastatic deposit
IV	Any T, Any N, M1	Irrespective of local tumor spread or nodal involvement, presence of distant metastasis

#### Table 2 Staging of pancreatic neuroendocrine tumors Involvement

AICC Stage

express fewer somatostatin receptors and hence may be missed on octreotide studies. Due to their high metabolic rate, they are better visualized on FDG-PET studies.<sup>20,52,54</sup> On imaging, these tumors show atypical enhancement patterns with decreased arterial enhancement and persistent or progressive enhancement of the tumor on venous phase imaging.<sup>55</sup> On MR, these tumors show lower ADC values with low enhancement in the arterial phase.<sup>24</sup> The presence of ill-defined margins, main pancreatic duct dilatation, vascular invasion, larger tumor size, and atypical enhancement pattern have been found

# Staging

The TNM staging AJCC UICC 8th edition is followed ( Table 2).58 Important points to note in the above-mentioned staging system are as follows:

to be associated with poorer histological grade.<sup>56,57</sup>

- 1. Tumors confined to the pancreas include those extending into the adjacent fat.
- 2. Regional lymph nodes are defined differently for tumors of the head and for tumors involving pancreatic body and tail. For neuroendocrine tumors of the pancreatic head, regional lymph nodes include common bile duct, common hepatic artery, portal vein, posterior and anterior pancreatoduodenal arcades, superior mesenteric vein, and right lateral wall of superior mesenteric vein nodes. Common hepatic artery, celiac axis, splenic artery, and splenic hilar lymph nodes are considered locoregional lymph nodes for pancreatic body/tail neuroendocrine tumors.
- 3. Metastatic disease is further subclassified as M1ametastasis confined to the liver; M1b-involvement of extrahepatic sites such as lung, ovary, nonlocoregional lymph node, peritoneum, and bone, and M1c, when there is involvement of both hepatic and extrahepatic sites.

## Management

The cornerstone of management of localized and resectable pancreatic neuroendocrine tumors is surgical resection. Adjuvant therapy after tumor resection does not have a proven role. Surgical treatment may be in the form of enucleation for small, well-defined tumors, resection of body/tail for distal tumors or pancreaticoduodenectomy/Whipple's procedure for tumors located in the pancreatic head.<sup>38,43,59,60</sup>

For metastatic disease, different treatment protocols have been tried. Surgical cytoreduction may aid in symptom reduction in functioning tumors as well as improve long-term survival.<sup>61</sup> Other treatment modalities which have been tried for liver metastases include transarterial chemoembolization, radioembolization, radiofrequency ablation (RFA), cryoablation, and percutaneous alcohol ablation.<sup>62-64</sup> No systematic reviews are available comparable these techniques; however, surgery is considered the standard approach for resectable liver lesions. If the lesions are not completely resectable, then RFA or other techniques mentioned above may be used for palliation of symptoms. If the lesions cannot be subjected to any of these, somatostatin analogs such as octreotide, octreotate, lanreotide, or edotreotide can be radiolabeled with 111 indium, 90 ytrium, or 177 lutetium for targeted radiotherapy.65,66

# Conclusion

Imaging plays an important role in detection, accurate characterization, and extent delineation of pancreatic neuroendocrine tumors. Future research these days is directed toward imaging prognostication and therapeutic response assessment.

#### **Conflict of Interest**

None declared.

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