Midgut Neuroendocrine Tumors: Imaging Assessment for Surgical Resection

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Midgut neuroendocrine tumors (MNETs) are rare tumors that arise in the jejunum, ileum, and proximal colon. Patients tend to present late, after a long history of vague nonspecific symptoms, and disseminated metastases are often discovered at presentation. However, the disease can run an indolent course, with a reported 5-year survival rate of more than 60% even in patients with disseminated liver metastases (1). Patients often die of complications caused by the primary tumor rather than of metastatic disease, which can remain stable throughout the course of the illness. Recent studies have shown a reduction in morbidity and mortality if the primary lesion is resected, even when there are disseminated metastases, because resection can prevent local complications such as small bowel obstruction and vascular occlusion. Metastases and secondary features such as desmoplasia and vascular involvement are often more easily demonstrated at imaging than is the primary tumor, which tends to be small (1–2 cm) and difficult to visualize.

Introduction

Midgut neuroendocrine tumors (MNETs) are rare tumors that arise in the jejunum, ileum, and proximal colon. Patients tend to present late, after a long history of vague nonspecific symptoms, and disseminated metastases are often discovered at presentation. However, the disease can run an indolent course, with a reported 5-year survival rate of more than 60% even in patients with disseminated liver metastases (1). Patients often die of complications caused by the primary tumor rather than of metastatic disease, which can remain stable throughout the course of the illness. Recent studies have shown a reduction in morbidity and mortality if the primary lesion is resected, even when there are disseminated metastases, because resection can prevent local complications such as small bowel obstruction and vascular occlusion. Metastases and secondary features such as desmoplasia and vascular involvement are often more easily demonstrated at imaging than is the primary tumor, which tends to be small (1–2 cm) and difficult to visualize.
MNETs represent 26% of diagnosed neuroendocrine tumors (NETs) (2) and are the second most-common small bowel malignancy after adenocarcinoma (3,4). The diagnosed incidence of NETs has risen in recent years from about one case per 100,000 in 1973 to about five cases per 100,000 in 2004 (2). The increase is thought to be due to a combination of factors, including improvements in tumor classification, increased detection levels with the more widespread use of endoscopic and radiologic investigations, and environmental and dietary factors (2).

We discuss the pathophysiology of MNETs, their imaging appearances, the surgical rationale for patients with MNETs, and the imaging criteria used to determine which tumors are potentially resectable.

Pathophysiology of NETs

NETs are a heterogeneous group of tumors that arise from a common precursor endocrine cell population that shares antigens with nerve elements, giving rise to the term neuroendocrine. These cells develop into the endocrine glands and cells of the diffuse neuroendocrine system. Diffuse neuroendocrine system cells are found scattered throughout the gut and produce a range of active substances involved in gut motility and function (3,5–7). MNETs arise from these cells in the gut and are most commonly found in the mid and terminal ileum.

NETs lack a uniform classification and grading system. Broadly speaking, NETs can be classified as well-differentiated slow-growing tumors (also known as carcinoids) or poorly differentiated tumors (small or large cell neuroendocrine carcinomas) that are generally highly malignant and aggressive (8) (Table 1).

Well-differentiated MNETs retain multipotent differentiation capacities, such as the ability to produce and secrete a variety of metabolically active substances. These substances include serotonin (5-hydroxytryptamine [5-HT]), which has mitogenic effects on fibroblasts, smooth muscle cells, and endothelial cells (9). MNETs can also produce growth factors such as vascular endothelial growth factor, which promotes angiogenesis, and prostaglandins and kinins, which can lead to local and systemic complications. Growth factors cause local fibrosis, resulting in desmoplasia of the surrounding mesentery that is demonstrated at computed tomography (CT). Desmoplasia can progress to small bowel obstruction, occlusion of the mesenteric vessels, and small bowel ischemia (3,10). Carcinoid syndrome (flushing, diarrhea, abdominal pain, and valvular heart disease) is caused when tumor factors (eg, 5-HT and kinins) reach the systemic circulation in patients with liver metastases (3).

The substances secreted by MNETs can be used for diagnosis. Useful markers that can be measured include urinary 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) and serum levels of the protein chromogranin A (found in secretory granules) (3). MNETs retain specific cell-membrane receptors, such as somatostatin receptors (SSTRs), that provide a pathway to localize and treat MNETs. Somatostatin is an endogenous regulatory peptide that binds to SSTRs to inhibit the release of bioactive peptides and amines such as serotonin. The SSTR pathway is used to image and treat MNETs with long-acting synthetic somatostatin analogs; the most commonly

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differentiation</th>
<th>Traditional Classification</th>
<th>ENETS and WHO 2010 Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade (&lt;2 mitoses/10 HPF, &lt;3% Ki-67 index)</td>
<td>Well differentiated</td>
<td>Carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 1 (G1)</td>
</tr>
<tr>
<td>Intermediate grade (2–20 mitoses/10 HPF, 3%–20% Ki-67 index)</td>
<td>Well differentiated</td>
<td>Carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 2 (G2)</td>
</tr>
<tr>
<td>High grade (&gt;20 mitoses/10 HPF, &gt;20% Ki-67 index)</td>
<td>Poorly differentiated</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3 (G3), small cell carcinoma</td>
</tr>
</tbody>
</table>

Large cell neuroendocrine carcinoma

Note.—ENETS = European Neuroendocrine Tumor Society, HPF = high-power field, WHO = World Health Organization.
Figure 1. Algorithm for imaging evaluation of a suspected MNET. FDG = fluorodeoxyglucose, MR = magnetic resonance, $^{111}$In = indium 111, PET = positron emission tomography, $^{68}$Ga = gallium 68.

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used analogs are octreotide and lanreotide (3,11). Another useful pathway is the norepinephrine uptake pathway; metaiodobenzylguanidine (MIBG), a synthetic norepinephrine analog, is taken up by the norepinephrine transporter in NETs (3). This pathway is used for MIBG scintigraphy and treatment.

**Imaging of MNETs**

Imaging is essential for initial diagnosis of MNETs, to guide management decisions, and for treatment follow-up. The radiologist must establish the location of the primary tumor and determine its resectability, the extent of metastatic disease, and any secondary complications. No single imaging modality can provide all of this information; radiologic evaluation requires a combination of imaging techniques (Fig 1).

Primary MNETs are usually small (<2 cm) and develop within the submucosal layer of the bowel wall. Up to one-third of cases involve multiple tumors, which are due to either the synchronous development of multiple tumors or submucosal metastatic spread (4,5,10,12).

**Imaging Modalities**

Historically, patients with a suspected MNET underwent barium studies of the small bowel, which have a low diagnostic yield for these small lesions and provide limited information about extraluminal disease. The increased spatial and temporal resolution of multidetector CT makes it an excellent modality for locating the primary lesion, staging the disease, and determining resectability. The highest sensitivity for detection of primary tumors is obtained by using dual-phase contrast-enhanced CT in addition to functional imaging with indium 111 ($^{111}$In) octreotide scintigraphy or gallium 68 ($^{68}$Ga) positron emission tomography (PET) (10,13). Magnetic resonance (MR) imaging can be used for patients who are unable to undergo contrast-enhanced CT. Video-capsule endoscopy (VCE) is being used increasingly to evaluate the small bowel, with a sensitivity of 60% for locating the primary tumor in patients with a metastatic MNET (14). These tumors can be difficult to visualize at VCE because of their small size and submucosal location. CT enterography has been shown to have a higher sensitivity than VCE for detection of tumors in the small bowel (15).

Reported sensitivities for primary tumor detection with CT are 50%–100% (16–18) and 43%–86% with $^{111}$In octreotide scintigraphy (17,19–21). More recent articles have reported higher sensitivities with the use of improved CT and functional imaging techniques.

**Barium Studies of the Small Bowel**

As stated previously, an MNET may be small and therefore undetectable at barium studies. An MNET may be seen at these studies as a small intraluminal filling defect. Later in the disease process, bowel wall thickening may be seen as the tumor extends through the layers of the bowel wall. Associated desmoplasia can result in tethering of bowel loops toward the mesenteric root, causing angulation and poor motility or evidence of obstruction at fluoroscopy (4) (Fig 2a). However, the sensitivity and specificity of barium studies are low, and extraluminal disease cannot be directly visualized.

**CT Examination**

CT can depict intraluminal and extraluminal bowel disease in addition to any nodal, liver, lung, or bone metastases. MNETs are typically found in the mid or terminal ileum. The tumors are usually vascular and enhance intensely with contrast material administration during the early arterial phase of imaging. Associated mesenteric nodes are often larger than the primary tumor and are more easily visualized at CT. If mesenteric nodes are seen, the primary tumor can often be located by following the mesentery to the adjacent small bowel loop (Fig 2c).

The CT technique used affects the conspicuity of the primary tumor and other lesions. At CT enterography, the patient is given a negative intraluminal contrast agent to distend the small bowel.
signal intensity on T2-weighted images and low signal intensity on T1-weighted images. Butylsco-polamine (Buscopan; Boehringer Ingelheim, Itapecerica, Brazil) is also used in our institution to reduce bowel motility (23). MR imaging can be used to localize the primary MNET and has better sensitivity and specificity for liver metastases than does CT, but its reduced spatial resolution may make small primary lesions difficult to visualize. MR imaging also is a more expensive and lengthier imaging examination than CT. Small primary tumors are better seen with MR enterography than with standard MR imaging and appear as nodular masses arising from the bowel wall. A primary tumor is best identified on gadolinium-enhanced images, where the avid enhancement increases conspicuity (4) (Fig 5).

Functional Imaging
Imaging of MNETs with radiopharmaceuticals utilizes the expression of specific receptors on cell surfaces. Functional imaging provides whole-body

Figure 2. Ileal NET in a 66-year-old woman with a mesenteric nodal mass, associated desmoplasia, and liver metastases. (a) Abdominal radiograph from a small bowel series shows desmoplasia (arrow) and separation of the bowel loops. The primary mass cannot be identified. (b, c) Coronal (b) and axial (c) portal venous phase CT images show the primary mass (black arrowhead in c), as well as desmoplasia (white arrow in b), mesenteric nodes (white arrowhead in b and c), and liver metastases (black arrow in b).

MR Imaging
MR imaging can also be used for assessing patients with an MNET. MR enterography uses a biphasic oral contrast agent (mannitol is used at our institution), and images are acquired in the late arterial phase (about 50 seconds after contrast agent administration) to provide optimal mucosal enhancement. This technique provides optimal conspicuity of MNETs, and lesions missed at standard CT (portal venous phase images without oral contrast agent administration) can often be depicted (Fig 3) (22).

At CT, the primary lesion appears as an arterially enhancing intraluminal mass, with associated mesenteric lymph nodes (which often show calcification), desmoplasia, and vascular encasement. Liver, peritoneal, lung, and bone metastases can also be visualized. The CT protocol used depends on the clinical indication for the examination (Table 2).

An arterial phase CT scan is necessary for assessment of liver metastases because they usually are hypervascular, show intense arterial enhancement, and may be isointense on portal venous phase images (Fig 4).
imaging with the potential to locate sites of unsuspected metastases, which is particularly important for patients being considered for curative resection. If functional imaging is positive for an MNET, this also predicts the therapeutic success of peptide receptor radionuclide therapy (PRRT) using yttrium 90 ($^{90}\text{Y}$) or lutetium 177 ($^{177}\text{Lu}$)–labeled somatostatin analogs (11,16) (Table 3).

The most commonly used functional imaging study is $^{111}$In octreotide scintigraphy, which has a detection rate of up to 90% for primary tumors or metastases (3,12,19,26). It utilizes $^{111}$In DTPA octreotide because octreotide is a long-acting somatostatin analog and binds to the SSTRs expressed by MNETs (3,11). SPECT/CT is preferred because the coregistration with CT allows indeterminate lesions to be correlated anatomically on the CT images (Fig 6). In addition, $^{111}$In octreotide scintigraphy can be used to assess the response to somatostatin analog treatment. Another agent used to image NETs is MIBG, a synthetic norepinephrine analog taken up by some NETs as it is incorporated into neurosecretory vesicles (3,16).
serotonin-producing tumors and has been shown to be sensitive for these tumors (3,25).

**Treatment**
The only curative treatment for MNETs is surgical resection of the primary tumor and any metastases. However, most patients present late with...
Figure 6. Terminal ileal NET in a 67-year-old woman. Axial $^{111}$In octreotide scan image fused with corresponding axial CT image (a) and axial fat-saturated gadolinium-enhanced T1-weighted MR image (b) show the primary tumor (arrow).

Table 3: Comparison of Functional Imaging Techniques and Therapies for MNETs

<table>
<thead>
<tr>
<th>Technique or Therapy</th>
<th>Isotope</th>
<th>Binding Agent</th>
<th>Receptor or Uptake Mechanism</th>
<th>Imaging Type</th>
<th>Time Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide scintigraphy</td>
<td>$^{111}$In</td>
<td>DTPA or DOTA and octreotide</td>
<td>SSTR 2, SSTR 5</td>
<td>SPECT/CT</td>
<td>24–48 h</td>
</tr>
<tr>
<td>MIBG scintigraphy</td>
<td>$^{123}$I</td>
<td>MIBG</td>
<td>Norepinephrine analog, VMAT</td>
<td>SPECT/CT</td>
<td>24 h</td>
</tr>
<tr>
<td>MIBG therapy</td>
<td>$^{131}$I</td>
<td>MIBG</td>
<td>Norepinephrine analog, VMAT</td>
<td>SPECT</td>
<td>24–72 h</td>
</tr>
<tr>
<td>$^{90}$Y therapy</td>
<td>$^{90}$Y</td>
<td>DOTATOC DOTATATE</td>
<td>SSTR</td>
<td>SPECT</td>
<td>24–72 h</td>
</tr>
<tr>
<td>$^{177}$Lu therapy</td>
<td>$^{177}$Lu</td>
<td>DOTATOC DOTATATE</td>
<td>SSTR</td>
<td>SPECT</td>
<td>24–96 h</td>
</tr>
<tr>
<td>FDG PET</td>
<td>$^{18}$F</td>
<td>FDG</td>
<td>Glucose analog</td>
<td>PET/CT</td>
<td>45–90 min</td>
</tr>
<tr>
<td>DOPA PET</td>
<td>$^{18}$F</td>
<td>DOPA</td>
<td>Catecholamine analog, LAT 1</td>
<td>PET/CT</td>
<td>45–90 min</td>
</tr>
<tr>
<td>Gallium PET</td>
<td>$^{68}$Ga</td>
<td>DOTATOC DOTANOC</td>
<td>SSTR 2,3,5</td>
<td>PET/CT</td>
<td>45–90 min</td>
</tr>
<tr>
<td>$^{11}$C 5-HTP PET</td>
<td>$^{11}$C</td>
<td>5-HTP</td>
<td>Serotonin synthesis</td>
<td>PET/CT</td>
<td>20 min</td>
</tr>
</tbody>
</table>

Source.—References 3, 12, 13, 16, 20, 22, 24, 25.
Note.—DOPA = dihydroxyphenylalanine, DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTANOC = DOTA Na$^+$ octreotide, DOTATATE = DOTA Tyr$^3$ octreotate, DOTATOC = DOTA Tyr$^3$ octreotide, DTPA = diethylene triamine pentaacetic acid (DTPA octreotide = pentetreotide), FDG = fluorodeoxyglucose, 5-HTP = hydroxytryptophan, LAT = large neutral amino acid transporter, SPECT = single photon emission CT, VMAT = vesicular monoamine transporter.

Nonsurgical Treatment

Nonsurgical treatment is useful for patients with unresectable or progressive disease and for symptom control. Somatostatin analogs such as octreotide and lanreotide block the release of bioactive amines, whereas interferon-α results in activation of enzymes that break down the metabolically active peptides and inhibit protein synthesis. These treatments can be used for carcinoid syndrome and provide good symptom control (11,12,28). Octreotide therapy has been shown to lengthen the time to tumor progression in patients with metastatic MNET (29) and may improve overall survival (2).
Cytotoxic chemotherapy is less useful because of the low mitotic rate of NETs but is sometimes useful for treating poorly differentiated NETs (3,11).

**Peptide Receptor Radionuclide Therapy**

PRRT can be used for patients with SSTR-expressing tumors (Fig 7). $^{90}$Y edotreotide and $^{177}$Lu octreotate have been used, with reported tumor...
response rates of up to 30% and a reduction in patient symptoms (11,30).

Treatment of Liver Metastases
In patients with liver metastases, wedge resection, lobar resections, and transplantation can be considered. However, patients often have extensive metastases that are deemed inoperable, in which case palliative options such as chemoembolization, arterial embolization, and radiofrequency ablation can be considered. These procedures may reduce symptoms, stabilize disease, and in some cases reduce tumor size to allow surgical resection (11,31).

Surgical Treatment

Rationale for Resection of the Primary Lesion
Although most patients with an MNET have metastatic disease at presentation, recent literature suggests that resection of the primary tumor provides some survival benefit (1,10,12,27,31). Patients with metastatic disease experience significant morbidity and mortality secondary to mesenteric desmoplasia and ischemia, and up to 15% of these patients will die of small bowel obstruction (27). It has been postulated that removal of the primary tumor at an early stage will prevent the development of small bowel complications.

Most tumors are unsuitable for radical resection or debulking, a cytoreductive surgery that involves resection of the greatest possible mass of tumor in the context of persistent metastases and is performed if 70%–90% of the tumor can be removed (1), because of extensive metastases. In these cases, resection of the primary MNET has been advocated, with resection of as many of the associated mesenteric lymph node metastases as possible. Resection may provide relief from local hormonal and tumor-related symptoms and limit further liver metastases (1).

Resectability Criteria
The main determinants of resectability are the degree of vascular involvement, desmoplasia, and patient comorbidities. CT is the best modality for assessment of vascular involvement and desmoplasi.

Vascular Involvement
The mesenteric nodes associated with MNET often follow the course of the superior mesenteric artery (SMA) and superior mesenteric vein (SMV) (Fig 9); these vessels can be encosed or
occluded by nodes (Fig 10). The degree of vascular involvement must be ascertained because it will determine whether resection is feasible (Fig 11).

Ideally, the primary bowel lesion and all abnormal nodes should be resected around the SMA, preserving the vascular supply and limiting bowel resection (10). Resection is usually feasible if a fat plane can be seen between the nodes and vessels at imaging (Fig 12). If smaller branches of the SMA are occluded distally, it may be possible to resect the segment of bowel supplied by that branch (Fig 11). It is important to determine how much bowel will need to be resected so that short bowel syndrome can be avoided (Fig 9). If a short segment of the more proximal SMA or SMV is occluded, resection may be possible, with vascular surgery to graft or stent the occluded section (32).
Bowel ischemia may be secondary to arterial or venous occlusion of the SMA or SMV (Fig 13). Abnormal bowel may manifest at imaging as wall thickening, increased or reduced bowel wall enhancement, and pneumatosis intestinalis (Fig 14).

**Desmoplasia**
MNETs can release local growth factors and other substances, resulting in extensive mesenteric fibrosis, or desmoplasia (3) (Fig 15). Desmoplasia leads to fixation of the mesentery with multiple fibrous bands and can cause small bowel obstruction and vascular occlusion (Fig 16). Regions of desmoplasia should be resected when possible to prevent development of an obstruction in the small bowel (Fig 17).

The approximate length of normal small bowel that will remain after surgery should be estimated. If the remaining length of small bowel will be less than 200 cm, surgery should be avoided because the patient will be at risk for developing short bowel syndrome, which causes diarrhea and malabsorption. Patients with short bowel syndrome may eventually require long-term total parenteral nutrition.

**Patient Comorbidities**
In addition to evaluation of the imaging findings, careful assessment should be made of the patient’s
 comorbidities, including those associated with the MNET (eg, carcinoid heart disease) and unrelated conditions such as diabetes and ischemic heart disease. These comorbidities will affect the timing and appropriateness of major surgery.

Carcinoid heart disease (Hedinger syndrome) is seen in up to 50% of patients with carcinoid syndrome (13). It is characterized by plaque-like fibrosis that affects the right side of the heart, including the tricuspid valve, pulmonary valve, cardiac chambers, vena cavae, and coronary sinus (Fig 18). The fibrosis is caused by serotonin and other fibrogenic factors that are released by the NET. These substances are inactivated by the lungs, hence the rarity of left-sided disease. Patients should be screened for carcinoid heart disease before major surgery is planned (13). At our institution, patients who require a valve replacement because of carcinoid heart disease undergo this procedure before major abdominal surgery if they are expected to survive more than 2 years.

An expert multidisciplinary team should evaluate the relative risks and benefits of major surgery to the patient, taking into account the imaging and pathologic findings and patient comorbidities.

**Conclusion**

Patients with metastatic MNETs often die of local complications of the primary tumor, such as small bowel obstruction or ischemia. These complications can potentially be avoided by resection of the primary tumor, with recent literature showing that resection has a survival benefit. CT and functional imaging are required to locate the primary tumor. Surgical resectability is determined after assessing vascular involvement and desmoplasia, factors best seen at CT, and patient comorbidities.
Figure 16. MNET in a 52-year-old man. Coronal portal venous phase CT image obtained with positive oral contrast material shows severe desmoplasia (white arrow) and mesenteric nodes (black arrow). Extensive abnormal, dilated, thick-walled small bowel loops are seen (arrowheads). The tumor was considered unresectable because of the insufficient length of unaffected small bowel.

Figure 17. MNET in a 38-year-old man. Coronal portal venous phase CT image shows severe desmoplasia (white arrow) and a mesenteric nodal mass (black arrow). Extensive abnormal, dilated, thick-walled small bowel loops are seen (arrowheads), with only a short length of normal small bowel remaining. The tumor was considered unresectable.

Figure 18. MNET in a 64-year-old woman. (a) Vertical long-axis balanced steady-state free precession (SSFP) cine MR image of the right heart obtained in diastole shows a restricted tricuspid valve opening (arrow) and liver metastasis (arrowhead). (b, c) Short-axis balanced SSFP cine MR images obtained in diastole (b) and systole (c) show tricuspid valve stenosis (arrow) and a central coaptation defect, with relatively little tricuspid valve movement from the diastolic image in b to the systolic image in c. (Case courtesy of Oliver Tann, MBBS, MRCP, FRCR, Great Ormond St Hospital, London, United Kingdom.)
References


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If functional imaging is positive for an MNET, this also predicts the therapeutic success of peptide receptor radionuclide therapy (PRRT) using yttrium 90 ($^{90}$Y) or lutetium 177 ($^{177}$Lu)–labeled somatostatin analogs.

The main determinants of resectability are the degree of vascular involvement, desmoplasia, and patient comorbidities. CT is the best modality for assessment of vascular involvement and desmoplasia.