Cross-sectional Imaging of Neuroendocrine Tumors of the Gastrointestinal Tract

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Disclosures

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Learning Objectives

• Review the classification of neuroendocrine tumors
• Recognize the CT and MR appearances of GI tract neuroendocrine tumors, mimics, and pitfalls
• Understand appropriate imaging strategies for identifying neuroendocrine tumors

Target Audience:

• Radiologists and Gastroenterologists
Background

• Neuroendocrine tumors (NETs) are epithelial neoplasms arising from enterochromaffin (neuroendocrine) cells.
• They can occur throughout the body, most commonly in the digestive and respiratory tract.
• Approximately 60 – 70% of NETs occur in the gastrointestinal (GI) tract, most frequently involving the rectum and small intestine where they can be multifocal.
Clinical Presentation

- Patients with NETs are often asymptomatic and incidentally detected, but they can present with a variety of symptoms such as:
  - bowel obstruction
  - obscure GI bleeding
  - bowel ischemia
  - carcinoid syndrome

- NETs generally demonstrate a site-specific phenotype and behavior so clinical symptoms depend on the location of the primary lesion and the presence or absence of metastatic disease.

- NET cells may secrete specific peptide hormones such as serotonin, insulin, gastrin, glucagon, somatostatin, etc., which can produce clinically evident hormonal syndromes.
Classification

- GI NETs are typically separated into two major categories:
  - Well-differentiated NETs
  - Poorly-differentiated NETs

- The 2010 WHO classification system divides well-differentiated NETs into low (G1) and intermediate grades (G2)—both are referred to as carcinoid tumors.

- Poorly differentiated NETs are high-grade (G3) carcinomas, associated with a far worse prognosis.
Ki67 is a large nuclear protein expressed during cell proliferation. Its exact function is unknown, but it appears to be involved in cell cycle regulation and is often used as a prognostic marker for NETs.

### Histology and Grading Systems for NETs

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ki-67 (%)</th>
<th>Mitoses/10 HPF</th>
<th>Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade (G1)</td>
<td>(\leq 2)</td>
<td>&lt;2</td>
<td>Neuroendocrine (Carcinoid) Tumor (G1)</td>
</tr>
<tr>
<td>Intermediate Grade (G2)</td>
<td>3-20</td>
<td>2-20</td>
<td>Neuroendocrine (Carcinoid) Tumor (G2)</td>
</tr>
<tr>
<td>High Grade (G3)</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Neuroendocrine Carcinoma (G3)</td>
</tr>
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Boudreaux et al. Pancreas 2010
**Grade 1** – Well-differentiated NET cells are relatively uniform and have round to oval nuclei with abundant granular cytoplasm. Cells are arranged in solid or trabecular clusters.

**Grade 2** – Similar to grade 1, with increased mitotic rate. Immunostaining enables identification of NET cells.

**Grade 3 Large cell** – Immunohistochemical expression of neuroendocrine markers is generally more limited in grade 3 NETs.

**Grade 3 Small cell** – Atypical mitoses, less cytoplasm, and a more sheet-like or diffuse architecture. Difficult to differentiate between small and large cell subtypes.
# Grading & Outcomes

Oncologic outcomes and treatment recommendations are dependent on tumor grade, site, size, depth of invasion, growth characteristics, and extent of disease (resectable or unresectable).

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Median Survival, months (95% CI)</th>
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<tbody>
<tr>
<td>Low-Grade (G1) Carcinoid Tumors</td>
<td>124 (101-147)</td>
</tr>
<tr>
<td>Intermediate-Grade (G2) Carcinoid Tumors</td>
<td>64 (56-74)</td>
</tr>
<tr>
<td>High-Grade (G3) Neuroendocrine Carcinomas</td>
<td>10 (9-11)</td>
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Boudreaux et al. Pancreas 2010
**Incidence**

- GI NETs are uncommon but not rare.
- The Surveillance Epidemiology and End Results (SEER, 1973–2004) registry showed an increasing incidence of small bowel NETs.
  - 2.1/million in 1973
  - 9.3/million in 2004
- The true incidence is likely much higher as hospitals are generally only required to report malignant cancers to state and national cancer registries, as a result many small localized NETs may be excluded from these registries.

*In 2000, NETs surpassed adenocarcinomas as the most common small bowel tumor reported to the National Cancer Data Base (NCDB 1985–2005).*

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Gross image with white mesenteric metastasis and mesenteric retraction, typical for NET.
Imaging

• The causes of the increasing incidence of GI NETs are unclear, but likely include improvements in and increased utilization of cross-sectional imaging and endoscopy. Increased physician awareness and possible environmental factors may also play a role.

• Specialized imaging techniques such as CT enterography and MR enterography offer improved sensitivity for detection of NETs.

• The variable imaging presentations of GI NETs will be reviewed, noting features that help to distinguish them from other GI neoplasms and mimics.
Invasive, hypermetabolic large cell NET in the distal esophagus. Esophageal NETs are exceedingly rare. They may be associated with adenocarcinoma or Barrett’s esophagus, but are difficult to prospectively differentiate from these diseases.

Invasive, poorly differentiated small cell NET in the distal esophagus, creating an abrupt high-grade stricture on esophagram and metabolically active on PET. Esophageal NETs most often occur in the distal esophagus.
Gastric

Type I somatostatin-avid **gastric carcinoid** lesions are often polypoid in nature.

**Gastrinomas** of stomach and pancreas with left parathyroid adenoma (type II)
Three types of gastric carcinoid tumors:

- **Type 1** – Most common subtype. Presents with multiple small lesions. Associated with hypergastrinemia secondary to chronic atrophic gastritis. Chronic atrophic gastritis can be due either to autoimmune gastritis, which is often associated with pernicious anemia, or secondary to chronic H. pylori infection. Lesions < 1 cm require no treatment.

- **Type 2** – Rare, also presents with multiple small lesions. Associated with Zollinger-Ellison syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN-1).

- **Type 3** – Sporadic subtype; no association with hypergastrinemia, chronic atrophic gastritis, autoimmune diseases, or MEN. Often presents with solitary gastric lesion and metastatic disease.

Binstock et al. AJR 2001
Duodenal gastrinomas in the setting of MEN-1. Lesions associated with MEN-1 are typically multiple and may present as intraluminal polyps or mural masses. They are associated with pituitary and parathyroid adenomas (calipers).
Duodenal

Sporadic NET of ampulla with associated bile duct obstruction. D-cell duodenal somatostatinomas are predominantly located in the periampullary region and have a unique clinical association with neurofibromatosis type I. Periampullary lesions may result in pancreatitis.

- Duodenal NETs are clinically and pathologically distinct from other small bowel NETs.
- Arise from either gastrin-producing G-cells (resulting in duodenal gastrinomas) or somatostatin-producing D-cells (resulting in duodenal somatostatinomas).
- Classic carcinoid syndrome is very rare with duodenal NETs because they do not arise from serotonin-producing enterochromaffin cells.
- G-cell duodenal gastrinomas may either be sporadic or associated with MEN-1 syndrome.
Small bowel NETs originate intramurally and may appear as hyperenhancing nodular or asymmetric plaque-like lesions with associated puckering or retraction of the bowel wall. The gross image shows white tumor with transmural extension and puckering.

Small bowel NETs are frequently multifocal (~25% of cases) and are most frequently found in the distal ileum. Early nodal metastases (arrow head) are intimately associated with mesenteric vessels and spread toward the mesenteric root.
Small bowel NETs have a propensity for nodal invasion along the bowel wall and mesenteric vessels. Mesenteric lymph node metastases often demonstrate a desmoplastic reaction due to local effects of secreted substances. The fibrosis can encase major mesenteric vessels and cause intestinal and mesenteric kinking and obstruction leading to dilated mesenteric veins and edematous intestinal loops. Involved intestinal segments can have a blue discoloration (white arrows) due to venous congestion and developing venous gangrene (blue bowel syndrome).
Small Bowel

Two patients with NETs in the ileum (example on left demonstrates associated serosal retraction (arrow head)) and active Crohn’s colitis involving the sigmoid colon. The association of Crohn’s disease and NETs is controversial, with several cases observed at our institution.

NETs can occur within Meckel’s diverticula as demonstrated with this small hyperenhancing carcinoid tumor.
Appendiceal NET causing focal **nodular thickening** of the appendix.

Small appendiceal NET with ruptured acute appendicitis.

- Most common type of appendiceal tumor.
- Usually small (<1 cm) and located in distal end of appendix.
- Most are discovered incidentally at time of appendectomy.
- Surgical management depends on tumor size:
  - <1 cm – appendectomy
  - 1-2 cm – appendectomy or right hemicolecotomy depending on histology and presence of local invasion or lymphadenopathy
  - >2 cm – right hemicolecotomy
Circumferential NET in the proximal ascending colon which directly invades into the adjacent pericolonic fat with local lymphadenopathy. Colonic/cecal carcinoids are often exophytic and large (>5 cm) at presentation. The gross specimen shows an invasive cecal mass extending into the ileocecal valve.
• Colonic NETs are most frequently found in the right colon, often at or near, the ileocecal valve.
• Patients can remain asymptomatic for extended periods unless bleeding occurs, which may account for later stage presentations.
• Aggressive tumors with high proliferation rate often present with lymph node and liver metastases.
• Surgical treatment is similar to colonic adenocarcinoma but with overall worse outcomes.
Rectal

- Large rectal NETs may be indistinguishable from adenocarcinoma by CT and MR imaging.
- An asymmetric mural mass may suggest the diagnosis.
- They are frequently asymptomatic and may be detected incidentally during colonoscopy.
- On CT or MR, rectal NETs may appear as small solitary submucosal nodules, multiple nodules, or a large polypoid ulcerating mass.
- Endoscopy and biopsy are required to confirm the diagnosis.
- Small tumors (< 1 cm) tend to be localized and can be treated by endoscopic resection.
Mimics – Enhancing GI masses

Hyperplastic polyp  Tubulovillous adenoma  Gastric GIST  Duodenal GIST

Breast Ca Mets  Lymphoma  Sclerosing mesenteritis
Mimics – NSAID Diaphragm Disease

Patient presenting with iron deficiency anemia and recurrent obstructive symptoms. CT enterography demonstrated multiple focal strictures, which were confirmed with capsule endoscopy. NSAID diaphragm disease can mimic both short inflammatory strictures in Crohn’s disease and plaque-like NETs, but these diseases usually demonstrate more asymmetric wall thickening.

Axial and coronal images with inset magnification demonstrate multiple mildly enhancing, circumferential strictures in the ileum.
Small bowel NET initially missed on routine CT performed with positive oral contrast. The same hyperenhancing, intraluminal mass clearly demonstrated on CT enterography performed with neutral oral contrast.

**Technical Issues:**

- Positive oral contrast – May obscure small lesions.
- Thicker image slices – Limit visualization of small lesions.
- Suboptimal tumor contrast:
  - Scan timing – NETs may be difficult to differentiate from bowel wall on venous phase.
  - Low kV imaging – May improve image contrast and decrease dose.
  - Injection rate – Higher injection rates (4-5 m/s) may improve tumor visualization.
### Pitfalls

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Enteric</th>
<th>Delayed</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Arterial Image" /></td>
<td><img src="image2.png" alt="Enteric Image" /></td>
<td><img src="image3.png" alt="Delayed Image" /></td>
</tr>
</tbody>
</table>

**Tiny small bowel NET** – best demonstrated on the enteric phase, but still visualized on the early arterial and delayed phases.

**High-flow AVM** – best seen on the arterial phase and not visualized on the delayed phase.

- Multiphase CT or MRI enterography may improved tumor visualization and help to distinguish NETs from other lesions based on enhancement characteristics.
Summary and Clinical Implications

• NETs can occur anywhere in the GI tract and represent the most common type of small bowel and appendiceal neoplasms.

• Understanding basic concepts regarding the pathologic classification of GI NETs and the ability to accurately characterize and stage NETs help radiologists and clinicians guide appropriate treatment and disease surveillance strategies.
Summary and Clinical Implications

• Frequently, small or early GI NETs may be subtle and overlooked, particularly on conventional cross-sectional imaging.

• Use of neutral oral contrast and multiphase CT and MR enterography aid detection of small GI NETs by optimizing luminal distention and tumoral enhancement.

• Although some of the CT and MR features of NETs are nonspecific, radiologists should be familiar with the common patterns and sites of disease involvement which can lead to the correct diagnosis.
References


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