Protocol for the Examination of Specimens From Patients With Neuroendocrine Tumors (Carcinoid Tumors) of the Small Intestine and Ampulla

Protocol applies to well-differentiated neuroendocrine tumors of the duodenum, ampulla, jejunum, and ileum. Carcinomas with mixed endocrine/glandular differentiation, poorly differentiated carcinomas with neuroendocrine features, and small cell carcinomas are not included.

Based on AJCC/UICC TNM, 7th Edition
Protocol web posting date: June 2012

Procedures
• Segmental Resection, Small Intestine
• Ampullectomy
• Pancreaticoduodenectomy, Partial or Complete, With or Without Partial Gastrectomy (Whipple Resection)

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Endocrine • Neuroendocrine Tumors of the Small Intestine and Ampulla
SmallBowelNET 3.2.0.0

CAP Small Bowel NET Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: SmallBowelNET 3.2.0.0

Summary of Changes
The following changes have been made since the February 2011 release.

Segmental Resection, Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)

Histologic Type
“Carcinoid tumor (low-grade neuroendocrine neoplasm)” was changed to “Well-differentiated neuroendocrine tumor (carcinoid tumor).”

Alternative Histologic Classification
This reporting element was deleted.

Histologic Grade
“(G3)” was added to the note.

Margins
“Required only if applicable” was added to “Other Margin,” “Ampullectomy Specimen,” and “Pancreaticoduodenal Resection Specimen,” and the data element “Not applicable” was deleted as appropriate, as follows:

Small Intestine Resection Specimen
...  
Other Margin(s) (required only if applicable)
Specify margin(s): ________________________________
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Ampullectomy Specimen (required only if applicable)
...
Pancreaticoduodenal Resection Specimen (for ampullary tumors) (required only if applicable)
...

Ancillary Studies
Reporting on Ki-67 was updated, changing >2% to 3% and adding “specify,” as follows:
+ ___ Ki-67 labeling index (specify: _____)
    + ___ ≤2%
    + ___ 3% to 20%
    + ___ >20%
**Explanatory Notes**

“Neoplasms” was changed to “tumors.”

**D. Histologic Type**

The first paragraph was changed to the following:

The World Health Organization (WHO) classifies neuroendocrine tumors as well-differentiated neuroendocrine tumors (either the primary tumor or metastasis) and poorly differentiated neuroendocrine carcinomas.\(^5\),\(^7\),\(^10\) Historically, well-differentiated neuroendocrine neoplasms have been referred to as carcinoid tumors, a term which may cause confusion because clinically a carcinoid tumor is a serotonin-producing tumor associated with functional manifestations of carcinoid syndrome.

**E. Histologic Grade**

“Mitotic count” was changed to “mitotic rate.”

Ki-67 Index (%): >2 was changed to 3.

The last sentence of the first paragraph was changed to:

The following grading system is recommended by the European Neuroendocrine Tumor Society (ENETS) and the WHO\(^10\),\(^12\):

**References**

Reference #10 was updated.
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

SMALL INTESTINE AND AMPULLA: Segmental Resection, Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
__ Duodenum
__ Ampulla of Vater
__ Small intestine
   + ___ Jejunum
   + ___ Ileum
   + ___ Unknown

Other organs received:
__ Stomach
__ Head of pancreas
__ Common bile duct
__ Gallbladder
__ Cecum
__ Right colon
__ Appendix
__ Other (specify): __________________________________
__ Not specified

Procedure
__ Segmental resection
__ Ampullectomy
__ Pancreaticoduodenectomy (Whipple resection)
__ Other (specify): _________________________
__ Not specified

+ Specimen Size (if applicable)
+ Specify: ___ (length) x ___ x ___ cm

Tumor Site (select all that apply) (Note B)
__ Duodenum
__ Ampulla
__ Small bowel
   + ___ Jejunum
   + ___ Ileum
__ Other (specify): _________________________
__ Not specified

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Tumor Size (Note C)
Greatest dimension: ___ cm (specify size of largest tumor if multiple tumors are present)
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see “Comment”)

Tumor Focality
___ Unifocal
___ Multifocal (specify number of tumors: _____)
___ Cannot be determined

Histologic Type (Note D)
___ Well-differentiated neuroendocrine tumor (carcinoid tumor)
+ ___ Somatostatinoma
+ ___ Gastrinoma
+ ___ Gangliocytic paraganglioma
+ ___ Other (specify): ____________________________

Histologic Grade (Note E)*
___ Not applicable
___ GX: Cannot be assessed
___ G1: Low grade
___ G2: Intermediate grade
___ Other (specify): ____________________________

* For poorly differentiated (high-grade) neuroendocrine carcinomas (G3) arising in the small intestine or ampulla, the College of American Pathologists (CAP) protocols for carcinomas of those organ sites should be used.1,2

Mitotic Rate
Specify: _____/10 high-power fields (HPF)
___ Cannot be determined

Microscopic Tumor Extension: Small Intestine
___ Cannot be assessed
___ No evidence of primary tumor
___ Tumor invades lamina propria
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades subserosal tissue without involvement of visceral peritoneum
___ Tumor penetrates serosa (visceral peritoneum)
___ Tumor directly invades adjacent structures (specify: ____________________)
___ Tumor penetrates to the surface of the visceral peritoneum (serosa) and directly invades adjacent structures (specify: ____________________)

Microscopic Tumor Extension: Ampulla
___ Cannot be assessed
___ No evidence of primary tumor
___ Tumor limited to ampulla of Vater or sphincter of Oddi
___ Tumor invades duodenal wall
___ Tumor invades pancreas
___ Tumor invades peripancreatic soft tissues
___ Tumor invades common bile duct
___ Tumor invades other adjacent organs or structures (specify): ____________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Margins

Small Intestine Resection Specimen

If all margins uninvolved by neuroendocrine tumor:
   Distance of tumor from closest margin: ___ mm or ___ cm
   Specify margin: ___________________________

Proximal Margin
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Distal Margin
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Mesenteric (Radial) Margin (Note F)
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Other Margin(s) (required only if applicable)
Specify margin(s): ___________________________
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Ampullectomy Specimen (required only if applicable)
___ Margins cannot be assessed
___ Margins uninvolved by neuroendocrine tumor
   Distance of neuroendocrine tumor from closest margin: ___ mm or ___ cm
   Specify margin (if possible): ___________________________
___ Margin(s) involved by neuroendocrine tumor
   Specify margin(s) (if possible): ___________________________

Pancreaticoduodenal Resection Specimen (for ampullary tumors) (required only if applicable)

If all margins uninvolved by neuroendocrine tumor:
   Distance of tumor from closest margin: ___ mm or ___ cm
   Specify margin: ___________________________

Proximal Mucosal Margin (Gastric or Duodenal)
___ Cannot be assessed
___ Uninvolved neuroendocrine tumor
___ Involved by neuroendocrine tumor

Distal Margin (Distal Duodenal or Jejunal)
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Pancreatic Retroperitoneal (Uncinate) Margin
___ Not applicable
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor (present 0-1 mm from margin)

Bile Duct Margin
___ Not applicable
___ Cannot be assessed
___ Margin uninvolved by neuroendocrine tumor
___ Margin involved by neuroendocrine tumor

Distal Pancreatic Resection Margin
___ Not applicable
___ Cannot be assessed
___ Margin uninvolved by neuroendocrine tumor
___ Margin involved by neuroendocrine tumor

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

+ Perineural Invasion
+ ___ Not identified
+ ___ Present
+ ___ Indeterminate

Pathologic Staging (pTNM) (Note G)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Tumor invades lamina propria or submucosa and size 1 cm or less (small intestinal tumors); tumor 1 cm or less (ampullary tumors)
___ pT2: Tumor invades muscularis propria or tumor size >1 cm (small intestinal tumors); tumor size >1 cm (ampullary tumors)
___ pT3: Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into nonperitonealized tissues
___ pT4: Tumor penetrates visceral peritoneum (serosa) or invades other organs

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Regional Lymph Nodes (pN)
___ Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in regional lymph nodes
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): ______________________

Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): ______________________

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
   + Specify site(s), if known: __________________________

+ Ancillary Studies (select all that apply) (Note H)
+ ___ Ki-67 labeling index (specify: ____)
   + ____ ≤2%
   + ____ 3% to 20%
   + ____ >20%
+ ___ Other (specify): __________________________
+ ___ Not performed

+ Additional Pathologic Findings (select all that apply) (Note I)
+ ___ Endocrine cell hyperplasia
+ ___ Tumor necrosis
+ ___ Psammoma bodies
+ ___ Mesenteric vascular elastosis
+ ___ Other (specify): __________________________

+ Comment(s)
Explanatory Notes

A. Application and Tumor Location
This protocol applies to well-differentiated neuroendocrine tumors (carcinoid tumors) of the small intestine and ampulla of Vater. Poorly differentiated neuroendocrine carcinomas, small cell carcinomas, and tumors with mixed glandular/neuroendocrine differentiation are not included.

Because of site-specific similarities in histology, immunohistochemistry, and histochemistry, neuroendocrine tumors of the digestive tract have traditionally been subdivided into those of foregut, midgut, and hindgut origin (Table). In general, the distribution pattern along the gastrointestinal (GI) tract parallels that of the progenitor cell type, and the anatomic site of origin of GI neuroendocrine tumors is an important predictor of clinical behavior.3

Site of Origin of Gastrointestinal Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Site</th>
<th>Foregut Tumors</th>
<th>Midgut Tumors</th>
<th>Hindgut Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stomach, Proximal Duodenum</td>
<td>Jejunum, Ileum, Appendix, Proximal Colon</td>
<td>Distal Colon, Rectum</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>86%-100% +</td>
<td>82%-92% +</td>
<td>40%-58% +</td>
</tr>
<tr>
<td>Neuron-Specific Enolase (NSE)</td>
<td>90%-100% +</td>
<td>95%-100% +</td>
<td>80%-87% +</td>
</tr>
<tr>
<td>Synaptophysin Serotonin</td>
<td>50% +</td>
<td>95%-100% +</td>
<td>94%-100% +</td>
</tr>
<tr>
<td></td>
<td>33% + 16,17</td>
<td>86% + 16,17</td>
<td>45%-83% + 4,6,17</td>
</tr>
<tr>
<td>Other Immunohistochemical Markers</td>
<td>Rare, + for pancreatic polypeptide, histamine, gastrin, vasoactive intestinal peptide (VIP), or adrenocorticotropic hormone (ACTH)</td>
<td>Prostatic acid phosphatase + in 20%-40% 16,17</td>
<td>Prostatic acid phosphatase + in 20%-82% 4,6,17</td>
</tr>
<tr>
<td>Carcinoid Syndrome</td>
<td>Rare</td>
<td>5%-39% 7,8</td>
<td>Rare</td>
</tr>
</tbody>
</table>

B. Site Specific Features
Duodenal NETs are relatively uncommon, accounting for roughly 4% of GI NETs.4 The most common subtype is the gastrin-secreting NET, or gastrinoma, associated with Zollinger-Ellison syndrome in one-third of cases.5 These gastrin-secreting tumors are often associated with multiple endocrine neoplasia type 1 (MEN1) syndrome, but sporadic tumors also occur.6 Duodenal somatostatin-producing tumors (somatostatinomas) are less common, accounting for about 1% of GI NETs, and are seldom associated with the functional syndrome of mild diabetes mellitus, cholelithiasis, and steatorrhea. These tumors often have a pure glandular growth pattern with scattered psammoma bodies and may be confused with conventional adenocarcinomas.7 They arise almost exclusively in the ampulla or periampullary duodenum and are often associated with MEN1 and with neurofibromatosis type 1.5

Most small bowel neuroendocrine tumors occur in the distal ileum. Multiple tumors are found in 25% to 40% of cases and may be associated with a worse outcome.8 Metastatic risk is increased by tumor size >2 cm, involvement of the muscularis propria, and mitotic activity.3

C. Tumor Size
For neuroendocrine tumors in any part of the gastrointestinal tract, size greater than 2.0 cm is associated with a higher risk of lymph node metastasis. For jejunoileal tumors, nodal metastases occur in about 12% of patients with tumors smaller than 1.0 cm and in most patients with tumors larger than 1.0 cm.3 Thus,
treatment for small bowel carcinoid tumor includes complete resection with regional lymphadenectomy.

D. Histologic Type
The World Health Organization (WHO) classifies neuroendocrine tumors as well-differentiated neuroendocrine tumors (either the primary tumor or metastasis) and poorly differentiated neuroendocrine carcinomas. Historically, well-differentiated neuroendocrine neoplasms have been referred to as carcinoid tumors, a term which may cause confusion because clinically a carcinoid tumor is a serotonin-producing tumor associated with functional manifestations of carcinoid syndrome.

Classification of neuroendocrine tumors is based upon size, functionality, site, and invasion. Functioning tumors are those associated with clinical manifestations of hormone production or secretion of measurable amounts of active hormone; immunohistochemical demonstration of hormone production is not equivalent to clinically apparent functionality.

Neuroendocrine Tumors of the Small Bowel

Well-Differentiated Neuroendocrine Tumor
Benign: Nonfunctioning cytologically bland tumors confined to mucosa or submucosa, with no angioinvasion, and measuring not more than 1 cm in greatest dimension.
Uncertain malignant potential: Nonfunctioning cytologically bland tumors confined to mucosa or submucosa, with or without angioinvasion, or greater than 1 cm in size. All gangliocytic paragangliomas without metastases are included in this category.

Well-Differentiated Neuroendocrine Carcinoma
Low-grade malignant potential: Nonfunctioning tumors that are larger than 2 cm or invade the muscularis propria or beyond or are metastatic. All functional tumors, such as small gastrinomas, are included in this category.

Histologic Patterns
Although specific histologic patterns in well-differentiated neuroendocrine tumors, such as trabecular, insular, and glandular, roughly correlate with tumor location, these patterns have not been clearly shown independently to predict response to therapy or risk of nodal metastasis and are rarely reported in clinical practice.

E. Histologic Grade
Cytologic atypia in low-grade neuroendocrine tumors has no impact on clinical behavior of these tumors. However, grading systems based on mitotic activity have been shown to have utility for foregut tumors. The following grading system is recommended by the European Neuroendocrine Tumor Society (ENETS) and the WHO:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Rate (per 10 HPF)</th>
<th>Ki-67 Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>≤2</td>
</tr>
<tr>
<td>G2</td>
<td>2 to 20</td>
<td>3 to 20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

* Mitotic rate should be based upon counting 50 high-power (40x objective) fields in the area of highest mitotic activity and reported as number of mitoses per 10 HPF.

** Ki-67 index is reported as percentage of positive tumor cells in area of highest nuclear labeling. It has been recommended that 2000 tumor cells be counted to determine the Ki-67 index; however, this practice may not be practical for routine clinical purposes, and it is acceptable to estimate the labeling index.
G1 and G2 are well-differentiated tumors with diffuse intense chromogranin/synaptophysin positivity. Punctate necrosis is more typical of G2 tumors. G3 tumors are high-grade neuroendocrine carcinomas (the CAP carcinoma protocol for the appropriate organ system should be used for poorly differentiated neuroendocrine carcinomas of the small intestine\(^1\) and ampulla\(^2\)).

F. Circumferential (Radial or Mesenteric) Margin
In addition to addressing the proximal and distal margins, assessment of the circumferential (radial) margin is necessary for any segment of gastrointestinal tract either unencased (Figure, C) or incompletely encased by peritoneum (Figure, B). The circumferential margin represents the adventitial soft tissue margin closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneal or subperitoneal aspect, respectively. The distance between the tumor and circumferential (radial) margin should be reported. The circumferential (radial) margin is considered negative if the tumor is more than 1 mm from the inked nonperitonealized surface but should be recorded as positive if tumor is located 1 mm or less from the nonperitonealized surface. This assessment includes tumor within a lymph node as well as direct tumor extension, but if circumferential (radial) margin positivity is based solely on intranodal tumor, this should be so stated.

The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by peritoneum (eg, jejunum and ileum) (Figure 1, A). Involvement of this margin should be reported even if tumor does not penetrate the serosal surface.

A. Mesenteric margin in viscus completely encased by peritoneum (dotted line). B. Circumferential (radial) margin (dotted line) in viscus incompletely encased by peritoneum. C. Circumferential (radial) margin (dotted line) in viscus completely unencased by peritoneum. Reproduced with permission from Washington et al.\(^{18}\) Copyright 2008. College of American Pathologists.

G. TNM and Stage Groupings
The TNM staging system for neuroendocrine tumors of the duodenum, ampulla, and small bowel of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.\(^{13}\)

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. \(pT\) entails a resection of the primary tumor or biopsy adequate to evaluate the highest \(pT\) category, \(pN\) entails removal of nodes adequate to validate lymph node metastasis, and \(pM\) implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest \(T\) and \(N\) categories or the \(M1\) category of the tumor can be
confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**TNM Descriptors**

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

**N Category Considerations**

The regional lymph nodes for the small intestine vary with site. For duodenal tumors, the regional lymph nodes are duodenal, hepatic, pancreaticoduodenal, infrapyloric, gastroduodenal, pyloric, superior mesenteric, and pericholedochal nodes. For ileal and jejunal tumors, the regional lymph nodes are the cecal (for tumors arising in the terminal ileum), superior mesenteric, and mesenteric nodes. Metastases to celiac nodes are considered distant metastases.

The regional nodes for the ampulla may be subdivided as follows:
- **Superior**: Lymph nodes superior to head and body of pancreas
- **Inferior**: Lymph nodes inferior to head and body of pancreas
- **Anterior**: Anterior pancreaticoduodenal, pyloric, and proximal mesenteric lymph nodes
- **Posterior**: Posterior pancreaticoduodenal, common bile duct or pericholedochal, and proximal mesenteric nodes

**TNM Anatomic Stage/Prognostic Groupings**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0#</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

* M0 is defined as no distant metastasis.

**H. Ancillary Studies**

Immunohistochemistry and other ancillary techniques are generally not required to diagnose well-differentiated neuroendocrine tumors. Specific markers that may be used to establish neuroendocrine differentiation include chromogranin A, neuron-specific enolase, synaptophysin, and CD56.\(^7\) Because of their relative sensitivity and specificity, chromogranin A and synaptophysin are recommended.

Immunohistochemistry for Ki-67 may be useful in establishing tumor grade (Note E) and prognosis\(^12\) but is
not currently considered standard of care.\(^7\)

Immunohistochemistry for specific hormone products, such as glucagon, gastrin, and somatostatin, may be of interest in some cases. However, immunohistochemical demonstration of hormone production does not equate with clinical functionality of the tumor.

I. Additional Pathologic Findings

Psammoma bodies are commonly found in duodenal neuroendocrine tumors, especially periampullary tumors\(^14\) expressing somatostatin and associated with von Recklinghausen disease.\(^5\)

Mesenteric vascular changes (elastic vascular sclerosis) associated with midgut carcinoids may produce arterial luminal narrowing due to concentric accumulation of elastic tissue in the adventitia. These vascular changes may lead to intestinal ischemia and frank necrosis.\(^15\)

References