# Diagnosis and staging of small bowel neoplasms

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Feb 22, 2023.**

## INTRODUCTION

Although the small bowel accounts for about 90 percent of the overall surface area of the gastrointestinal (GI) tract, tumors of the small bowel are rare, comprising approximately 3 to 6 percent of all GI neoplasms, <5 percent of GI malignancies, and about 0.6 percent of cancers in the United States [1]. A variety of tumors, both malignant and benign, may arise within the small intestine. Malignant tumors include adenocarcinomas, neuroendocrine tumors (carcinoids), stromal tumors and other sarcomas, and lymphomas. Benign lesions that may arise in the small bowel include adenomas, leiomyomas, fibromas, and lipomas.

Metastatic lesions from malignancies such as melanoma, lung, breast, cervix, and colon can also involve the small bowel, as can neoplasms associated with polyposis syndromes such as familial adenomatous polyposis syndrome or Peutz-Jeghers syndrome, and diseases such as Crohn and celiac disease. These are discussed elsewhere. (See "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management" and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults" and "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

The diagnosis and staging of small bowel tumors will be reviewed here. The epidemiology, clinical manifestations, and treatment of the specific types of tumors are discussed separately. (See "Epidemiology, clinical features, and types of small bowel neoplasms" and "Treatment of small bowel neoplasms".)

## CLINICAL FEATURES

Typically, patients with small intestinal tumors of any type present either with an incidental mass on abdominal imaging or after developing signs and/or symptoms of intestinal disease.

These may include one or more of the following:

- Abdominal pain
- Small bowel obstruction (manifesting as nausea and/or vomiting or, in the case of a duodenal primary, the additional symptom of jaundice)
- Bleeding (manifesting as overt bleeding or unexplained iron-deficiency anemia)
- Anorexia and/or unintentional weight loss
- Bowel perforation (manifesting as acute abdominal pain and signs and symptoms of peritoneal infection)

In addition, patients with lymphoma may present with systemic "B" symptoms (ie, fever, weight loss, drenching night sweats). Malignant tumors are more likely to be symptomatic as compared with benign lesions. (See "Epidemiology, clinical features, and types of small bowel neoplasms", section on 'Clinical presentation' and "Clinical presentation and initial evaluation of non-Hodgkin lymphoma", section on 'Systemic "B" symptoms'.)

The variable nature of the presenting symptoms, combined with the general lack of physical findings, can contribute to a delay in diagnosis in many cases. Prior to the advent of specific small bowel imaging and endoscopic techniques, lag time between initial presentation and diagnosis could be significant, with a reported mean of 18 months for malignant tumors and three years for benign lesions in some studies [2]. More recently, an analysis in patients with localized small bowel adenocarcinoma noted a much shorter median time from initial medial evaluation to diagnosis (31 days, range 1 to 390 days) [3]. However, even in contemporary series, the appropriate discovery of small bowel neuroendocrine tumors (NETs) can take up to 36 months for definitive diagnosis [4]. (See 'Neuroendocrine tumors' below.)

As prognosis is closely linked to disease extent for all of the major malignant small bowel tumors, early detection and treatment can contribute to a favorable outcome [5,6]. However, given the nonspecific nature of the presenting symptoms, a high index of suspicion is essential for early diagnosis and treatment [7,8].

## DIAGNOSTIC EVALUATION

Patients with symptoms suggestive of a small bowel neoplasm and patients with an incidental finding on cross-sectional imaging done for another reason where a small bowel tumor is part of the differential diagnosis should undergo a complete history and physical examination. A minimum laboratory workup should include a complete blood count with differential, measurement of serum electrolytes, liver function tests, and fecal occult blood test as warranted.

The specific components of the subsequent diagnostic and staging workup depend on the clinical presentation, and are addressed in the following sections. For most patients, we base our initial workup on the clinical presentation.

**General approach to patients with suggestive symptoms** — There is no single method that is recommended as best for imaging of the small intestine in a patient with a suspected small bowel tumor. Dedicated small bowel cross-sectional imaging using computed tomography (CT) and magnetic resonance imaging (MRI), and endoscopic techniques including video capsule endoscopy (VCE), push enteroscopy, and device-assisted enteroscopy (double balloon and single balloon enteroscopy or spiral enteroscopy) are options that may be complementary in establishing a diagnosis. One retrospective study of 257 patients with localized small bowel adenocarcinoma showed that in 197 patients whose diagnostic modalities were known, the diagnosis was made by endoscopy in 38 percent, during surgery in 35 percent, with radiographic imaging in 21 percent, and via VCE in 6 percent [3]. A single diagnostic procedure, however, may be insufficient for a definitive diagnosis, and multiple tests may be needed sequentially to evaluate the small intestine adequately.

Although there is no established best initial testing strategy or sequence of diagnostic tests in general, for patients with a suspected small bowel tumor, it is reasonable to start with the least invasive modality such as VCE if there are no obstructive symptoms, or with dedicated cross-sectional imaging, if obstructive symptoms are present [9]. However, guidelines are not definitive on this issue. (See "Wireless video capsule endoscopy" and "Overview of deep small bowel enteroscopy".)

A suggested approach to patients with specific symptoms is outlined in more detail below. (See 'Our approach to patients with specific symptoms' below.)

**Patients with incidental findings** — Because of the rarity of small intestinal neoplasms, there is no recommended population-based screening for any of the tumors that arise in the small bowel. Thus, incidental tumors tend to be detected only in the setting of cross-sectional imaging being performed for unrelated reasons (eg, back pain, kidney stones). In this setting, our diagnostic approach is outlined in the algorithm ( algorithm 1) and summarized below:

- If imaging suggests a small intestinal mass and there is no evidence of metastatic disease, we recommend the appropriate endoscopic evaluation (esophagogastroduodenoscopy [EGD], push enteroscopy, ileocolonoscopy, or device-assisted enteroscopy depending on the location of the lesion) in order to visualize the mass and obtain tissue for pathologic diagnosis.

  EGD is typically only able to examine through the second portion of the duodenum, while push enteroscopy can advance into the most proximal parts of the jejunum. Ileocolonoscopy allows examination of the most distal part of the ileum (terminal ileum). Because of its capacity to advance deeply into the small bowel, device-assisted enteroscopy may be the endoscopic procedure of choice. From an antegrade (oral) approach, it may reach as far as the distal jejunum and proximal ileum, and from a retrograde (anal) approach, this technique may allow access to the mid-distal ileum. The success of deep enteroscopy, however, is variable even in expert hands, depending on patient anatomy, endoscopic approach, endoscopist experience and skills, and available facilities. (See "Overview of upper gastrointestinal endoscopy (esophagogastroduodenoscopy)" and "Overview of colonoscopy in adults" and "Overview of deep small bowel enteroscopy".)

- If endoscopic evaluation is complete and unremarkable, and if suspicion for invasive malignancy is low, we recommend close follow-up with short-interval (eg, three months) cross-sectional imaging.

- If endoscopic evaluation is incomplete, and there is no evidence of obstruction, VCE is recommended for visualization of areas not accessed by endoscopy, although tissue cannot be sampled using this approach.

  If suspicion is high for an invasive malignancy, options for further workup include:

  - CT enterography.

  - Integrated fluorodeoxyglucose-positron emission tomography/CT (FDG PET/CT). This study may be helpful for lesions that are of sufficient size to be functionally detected, generally >1 cm. However, FDG uptake can also occur with inflammation, and PET scanning generally does not help narrow the differential diagnosis. (See 'Integrated PET/CT' below.)

  - Somatostatin receptor-based imaging (eg, Gallium Ga-68 DOTATATE PET). This study may be helpful for suspected small bowel neuroendocrine tumors (NETs), but we generally reserve this approach for symptomatic patients with diarrhea and/or

cutaneous flushing in whom there is suspicion for carcinoid syndrome, especially if the results of cross-sectional imaging are consistent with this diagnosis. (See 'Our approach to patients with specific symptoms' below and 'Somatostatin receptor-based imaging' below.)

- Intraoperative enteroscopy (IOE) or laparoscopy/surgical exploration. In some cases, this invasive approach may be needed to establish the diagnosis. (See 'Surgical exploration' below.)

- Assessment of tumor markers including carbohydrate antigen (CA) 19-9, carcinoembryonic antigen, chromogranin A, urinary levels of 5-hydroxyindoleacetic acid [5-HIAA], or others is generally not recommended due to low positive predictive value, and the lack of specificity and sensitivity for most of these tests in the setting of early stage disease. (See 'Tumor markers' below.)

**Our approach to patients with specific symptoms** — Our approach to symptomatic patients depends on the predominant symptom.

**Abdominal pain** — Abdominal pain of variable duration and quality is the most common symptom of a small bowel neoplasm (see "Epidemiology, clinical features, and types of small bowel neoplasms"):

- If there is suspicion that abdominal pain is due to a small bowel neoplasm, the initial evaluation should include cross-sectional imaging (ie, CT abdomen/pelvis) with intravenous (IV) contrast, provided no contraindications exist. This is often performed shortly after presentation, especially in acute care settings.

- If there is no apparent small bowel lesion or apparent metastatic disease, and suspicion remains high for a neoplasm, direct endoscopy (EGD and/or colonoscopy) may be the next step. Malignancies of the upper gastrointestinal (GI) tract and colon are more common than small bowel tumors and should be excluded as a source of abdominal pain.

- If a lesion is identified, it must be biopsied to allow for accurate diagnosis and to guide management. Biopsy should use the least invasive means possible; percutaneous biopsy may be used to sample suspected metastases, and an endoscopic approach may be used to biopsy a putative primary. If a lesion is accessible with a push enteroscopy or ileocolonoscopy, these procedures should be employed. If the lesion is deeper in the small bowel, device-assisted enteroscopy is the recommended approach depending on the patient's clinical status and available resources. (See "Overview of deep small bowel enteroscopy".)

- If no lesion is identified on cross-sectional imaging or direct endoscopies and suspicion remains high for a neoplasm, VCE may be used as the next step, as long as obstructive symptoms are absent, but tissue cannot be obtained using this approach.

  Notably, despite advances and expansions in available diagnostic modalities that target the small bowel, there remains a distinct possibility that these measures may not establish a definitive diagnosis. In such cases, if a strong suspicion for invasive cancer (eg, persistent unexplained abdominal pain, iron-deficiency anemia, weight loss) remains, surgical referral may be appropriate for consideration of diagnostic laparoscopy/surgical exploration or intraoperative enteroscopy. However, if suspicion for malignant etiology is low, follow-up imaging and/or endoscopy with evaluation of blood counts and complete metabolic panel within 6 to 12 weeks may also be reasonable.

**Unintentional weight loss/anorexia** — The differential diagnosis for unintentional weight loss/anorexia is broad in the absence of any other common symptoms mentioned above. The overall approach is reviewed in detail elsewhere. (See "Approach to the patient with unintentional weight loss".)

**Bowel obstruction** — Bowel obstructions may occur with benign and/or malignant neoplasms affecting the small bowel ( table 1). The differential diagnosis should also include lesions extrinsic to the small bowel (eg, adenopathy, hernia, volvulus, adhesions from prior small bowel surgery), and non-malignant intrinsic causes (eg, intramural hemorrhage, intussusception) ( table 1). (See "Etiologies, clinical manifestations, and diagnosis of mechanical small bowel obstruction in adults".)

Symptoms typically include abdominal pain, nausea/vomiting, early satiety, and constipation, although watery overflow diarrhea is possible with high-grade partial obstructions. Typically, patients will present in the acute care setting and have cross-sectional imaging (often CT abdomen/pelvis) already performed showing a transition point at the site of the primary with or without clear evidence of a mass. (See "Etiologies, clinical manifestations, and diagnosis of mechanical small bowel obstruction in adults".)

As the majority of bowel obstructions do not reflect malignant disease, initial steps include:

- Detailed review of radiographic imaging for areas that are concerning for a mass or regional lymph nodes at the site of obstruction.

- Careful assessment of patient's history regarding clinical symptoms and signs concerning for malignancy, including unexplained iron-deficiency anemia or chronic weight loss, cutaneous flushing, or the presence of "B" type systemic symptoms (ie, fever, night sweats,

weight loss) that may raise concern for lymphoma. (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas".)

For proximal or very distal masses in the small bowel, EGD and/or ileocolonoscopy can be conducted for examination, biopsy, and definitive diagnosis. Push enteroscopy and device-assisted enteroscopy techniques can be considered if EGD/ileocolonoscopy are unrevealing, but VCE is contraindicated and should be strictly avoided in patients with suggestion of small bowel obstruction to avoid retention and impaction of the capsule at the site of obstruction. Capsule retention may necessitate surgical or endoscopic retrieval. (See 'Enteroscopy' below and "Wireless video capsule endoscopy", section on 'Contraindications'.)

Most patients with neoplastic tumors presenting with obstruction will require definitive or palliative surgical intervention; however, those patients diagnosed with small intestinal lymphoma are likely to respond rapidly to induction chemotherapy, thus supporting the effort to determine histologic diagnosis in the least invasive manner possible. (See "Initial treatment of limited stage diffuse large B cell lymphoma", section on 'Other extranodal sites' and "Treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)", section on 'Small intestine MZL'.)

**Bowel perforation** — Bowel perforation is a rare presenting symptom of small bowel neoplasm. (See "Epidemiology, clinical features, and types of small bowel neoplasms".)

In most cases, the patient will present in the acute care setting and have cross-sectional imaging (often CT abdomen/pelvis) already performed showing intraperitoneal free air, evidence of abscess associated with the intestinal wall, signs of peritonitis, with or without clear evidence of a mass. Further diagnostic studies are not generally indicated, and endoscopy, in particular should be generally avoided.

Most patients will be managed surgically to repair the defect. Some are managed conservatively if evidence suggests spontaneous closure of the perforation or if there are patient-specific medical comorbidities precluding surgery, or if goals of care do not support surgical intervention. Tissue should be obtained at the time of surgery to provide a histologic diagnosis.

**Chronic diarrhea with or without cutaneous flushing** — Patients with well-differentiated NETs often present with symptoms similar to those of other small bowel tumors. However, they may also become symptomatic from hormones secreted by the tumor cells, particularly when metastatic disease, almost always to the liver, is present. For most small bowel NETs the predominant symptoms of carcinoid syndrome are diarrhea, with or without cutaneous flushing. (See "Clinical features of carcinoid syndrome".)

For such patients, we recommend initial evaluation with dual phase (arterial and portal venous) contrast-enhanced helical CT of the abdomen and pelvis. If a small bowel NET is suspected based upon imaging characteristics, tissue should be obtained via percutaneous biopsy of a suspected metastatic lesion. For apparent localized disease, tissue of the small bowel mass can be obtained endoscopically via EGD and/or ileocolonoscopy, or with advanced enteroscopic or surgical approaches when needed. (See 'Computed tomography scan' below.)

For patients with histologic confirmation of well-differentiated NET, somatostatin-receptor based imaging (eg, gallium Ga-68 DOTATATE PET/CT) is needed for staging. (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Imaging'.)

**Jaundice** — In the setting of new-onset jaundice with direct (conjugated) hyperbilirubinemia, only two scenarios implicate a small bowel neoplasm as the underlying cause:

- A primary duodenal mass involving the second portion of the duodenum and compressing the common bile duct or obstructing the ampullary orifice
- A significant burden of hepatic or porta hepatis metastases of small intestinal origin

These findings are usually seen on initial cross-sectional imaging. A periampullary mass in this location might represent a primary duodenal adenocarcinoma, a distal cholangiocarcinoma, an ampulla of Vater carcinoma, or a pancreas cancer in the head that is invading the duodenum. Radiographic imaging may not enable this distinction, and EGD with or without endoscopic ultrasound is indicated for diagnosis and disease staging when duodenal masses are present (see 'Upper endoscopy/EUS' below and "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging", section on 'Diagnosis and staging' and "Clinical manifestations and diagnosis of cholangiocarcinoma", section on 'Clinical presentation' and "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer"). When jaundice is present, endoscopic retrograde cholangiopancreatography is necessary to attempt biliary decompression and can provide tissue for cytologic/pathologic diagnosis. Magnetic resonance cholangiopancreatography may further assist in ascertaining the primary tumor site of origin if this is otherwise not evident on the aforementioned studies, and if doing so might influence treatment decisions.

**GI tract bleeding** — Gastrointestinal (GI) tract bleeding may be occult or overt.

- **Occult gastrointestinal bleeding or suspected small bowel bleeding** – Occult GI bleeding is defined as GI bleeding that is not clinically visible, usually presenting as an unexplained iron deficiency anemia. Suspected small bowel GI bleeding is GI bleeding in

which no bleeding source is identified after performing both upper and lower endoscopy [10]. It can be occult or overt. A diagnostic algorithm for obscure small bowel bleeding is available ( algorithm 2).

Following upper and lower endoscopies and exclusion of other causes of iron-deficiency anemia, a small bowel evaluation should be conducted to determine if the small bowel is the site of potential GI blood loss. In the absence of obstruction, the first-line diagnostic tool for the evaluation of small bowel bleeding is VCE [11,12]. Subsequently, or as an alternative, a multiphasic CT enterography (CTE), with occult GI bleed protocol is an option. This study is done with oral contrast, and acquires images prior to giving iodinated IV contrast, as well as during arterial and portal venous phases after IV contrast administration. (See 'Computed tomography scan' below.)

However, absence of a small bowel abnormality using a multiphasic occult GI or suspected small bowel bleeding CTE protocol [10] is not sufficient to exclude a small bowel abnormality. If not previously performed, in this setting VCE should be conducted to provide a complete evaluation of the small bowel lumen. (See "Evaluation of occult gastrointestinal bleeding" and "Evaluation of suspected small bowel bleeding (formerly obscure gastrointestinal bleeding)".)

- **Overt gastrointestinal bleeding** – Patients presenting with hematemesis, melena, or hematochezia should have a workup appropriate for the acuity and severity of bleeding. An algorithmic approach to evaluation of patients presenting with upper GI tract bleeding ( algorithm 3) or hematochezia ( algorithm 4) are provided. (See "Approach to acute upper gastrointestinal bleeding in adults" and "Approach to acute lower gastrointestinal bleeding in adults".)

  Generally, EGD and/or ileocolonoscopy will be performed soon after clinical presentation and may reveal a primary duodenal or distal ileal neoplasm, provided the lumen is sufficiently well visualized and not obscured by blood products. If visualization is poor, then repeat endoscopy following clearance of blood products may be needed.

  If EGD/ileocolonoscopy are unrevealing in a patient with overt GI bleeding, cross-sectional imaging should be performed, typically CT angiography (multiphasic CT with IV contrast and no oral contrast). (See 'Computed tomography scan' below.)

  Depending on imaging findings, advanced endoscopy (eg, device-assisted enteroscopy) or VCE are reasonable next approaches. In particular, VCE may be useful if all other intraluminal and radiographic investigations fail to reveal the primary bleeding site.

However, tissue cannot be obtained using this approach. (See "Overview of deep small bowel enteroscopy".)

## OVERVIEW OF AVAILABLE DIAGNOSTIC TESTS

**Radiographic imaging** — Multiple radiographic investigations are available for patients suspected of having a small bowel tumor ( table 2). Plain abdominal films are generally of limited value unless bowel obstruction is suspected, although this finding is nonspecific. Enteroclysis or double-contrast radiographic study represent historical options that have been replaced by cross-sectional imaging.

**Computed tomography scan** — A CT scan is frequently obtained when evaluating vague or indeterminate abdominal complaints [10]. In the absence of active bleeding, this is typically CT enterography, a single phase CT of the abdomen and pelvis with a neutral oral contrast agent that distends the bowel but has no density, thus facilitating the visualization of a mass within the bowel lumen. (See 'Somatostatin receptor-based imaging' below.)

For active GI bleeding, the preferred protocol is a multiphasic GI bleeding study, in which images are acquired prior to administration of intravenous (IV) contrast, as well as during the arterial and portal venous phases after contrast administration, and is performed either without (CT angiography) or with (CT enterography [CTE] protocol) oral contrast [10]. In such cases, oral contrast is not recommended for overt GI bleeding, only for occult GI bleeding.

- **Single phase CT enterography** – During a single phase CT enterography study patients rapidly ingest a large volume (1.5 to 2 L) of an attenuation-neutral enteric contrast material (often low-concentration barium) [10]. This results in distension of the small bowel lumen with a contrast agent that does not interfere with the ability to visualize the lumen and the bowel wall with CT. This approach should be used with caution in patients with high-grade bowel obstruction unless they have established alternate means to vent the solution.

  CT is able to detect abnormalities in approximately 70 to 80 percent of patients with small bowel tumors [13,14]. Besides demonstrating the primary tumor, CT scans are of critical importance for appropriate evaluation of extraintestinal spread to distant sites and involvement of regional lymph nodes. In addition, specific radiographic features may suggest the histologic diagnosis [15-17].

  - In one of the largest series, 219 patients with a clinical suspicion for a small bowel neoplasm and a negative upper- and lower-endoscopic evaluation underwent contrast and water-enhanced CT enterography [17]. Positive findings were compared with the

results of surgical exploration or endoscopic procedures, while negative results were correlated with the results of surgery, intraoperative enteroscopy, capsule endoscopy, or clinical follow-up.

A small bowel mass was demonstrated in 55 patients, which was confirmed in 50 patients (ie, there were five false-positive studies). These included two masses diagnosed as fold thickening at preoperative enteroscopy, two small bowel polyps, and one 18 mm hyperintense mass, with all three cases confirmed as normal mucosa at surgery or preoperative enteroscopy. Of the 164 patients with a normal result, a small bowel tumor was later found in nine. The sensitivity, specificity, negative predictive value, and positive predictive value were 85, 97, 95, and 91 percent, respectively. Whether similar results can be achieved at other centers is unclear.

At least some data for a small study of 17 patients suggest that CT enterography is more sensitive for detecting small bowel tumors than wireless video capsule endoscopy (VCE) [18].

- **Occult GI bleeding CT** – For patients with suspected occult GI bleeding who are not undergoing VCE, the preferred radiologic imaging protocol is a multiphasic occult GI bleeding study, which is performed with oral contrast in addition to acquisition of images prior to administration of IV contrast, as well as during the arterial and portal venous phases after contrast administration [10]. This is frequently referred to as a CT enterography (CTE) protocol. In a meta-analysis of 18 studies, the yield of a CTE protocol for detecting a source of suspected small bowel bleeding was 40 percent (95% CI 33-49 percent) [19]. The yield appears to be highest in patients with a history of massive bleeding [20]. (See "Evaluation of suspected small bowel bleeding (formerly obscure gastrointestinal bleeding)", section on 'Enterography'.)

- **Role of chest CT** – For small bowel neoplasms, CT chest should be conducted for complete staging. For most lymphomas, fluorodeoxyglucose (FDG) PET/CT is more sensitive and specific in detecting the initial extent of disease (except in cases of small lymphocytic lymphoma and marginal zone lymphoma) and is recommended for initial assessment and monitoring treatment efficacy [21]. (See "Pretreatment evaluation and staging of non-Hodgkin lymphomas".)

**MRI of the abdomen and pelvis and MRCP** — Magnetic resonance imaging (MRI) of the abdomen and pelvis is an alternative for cross-sectional imaging with contrast-enhanced CT where there is a contraindication to CT contrast. Magnetic resonance cholangiopancreatography (MRCP) may be needed in the initial workup of a suspected

duodenal malignancy to further ascertain the tumor site of origin, particularly in the presence of biliary obstruction.

**Upper gastrointestinal series with small bowel follow-through** — Upper gastrointestinal (GI) series with small bowel follow-through (UGI/SBFT) is an older test that may show a mass lesion, mucosal defect, or intussusception. In older series, the sensitivity was approximately 50 to 60 percent for the detection of advanced small bowel tumors [22-24]. However, sensitivity for primary benign tumors is as low as 25 percent [24]. Advanced endoscopic techniques have largely replaced the role of UGI/SBFT.

**Angiography and radionuclide scanning** — In patients with active bleeding, angiography or radionuclide scanning with technetium (99mTc) sulfur colloid or 99mTc pertechnetate-labeled autologous red blood cells can help to localize the site of bleeding if the rate of bleeding is sufficiently high. In addition, for certain tumors, most notably neuroendocrine tumors (NETs) and leiomyosarcoma, a distinctive tumor blush may be seen on angiography. However, these tests are rarely indicated in the initial diagnostic workup, and instead, are restricted to situations where other tests have not been revealing. (See "Evaluation of suspected small bowel bleeding (formerly obscure gastrointestinal bleeding)", section on 'Radionuclide scanning' and "Evaluation of suspected small bowel bleeding (formerly obscure gastrointestinal bleeding)", section on 'Angiography'.)

**MR enterography** – Magnetic resonance (MR) enterography is an alternative to CT enterography, but in our view, there is insufficient information on its accuracy to detect small bowel tumors to warrant its use. MRI has the advantage of not using ionizing radiation, which allows for sequential imaging of the small bowel. Like CT enterography, a neutral contrast agent (often polyethylene glycol) is used to distend the small bowel. Intraluminal and extraluminal MR findings, combined with the presence of contrast enhancement and functional information, may permit characterization of small bowel neoplasms.

Although not as widely available as CT enterography, the available data on MR enterography for diagnosis and exclusion of a small bowel neoplasm are as follows [7,25,26]:

- One study included 91 symptomatic patients with either suspected or established small bowel disease [7]. The cases were independently interpreted by two different GI radiologists who were blinded as to the clinical history. Eighty-six of the exams were correctly interpreted (diagnostic accuracy 95 percent); a small bowel neoplasm was confirmed histopathologically (by endoscopy or surgery) in 32. The sensitivity, specificity, positive predictive value, and negative predictive value were 94, 95, 91, and 97 percent,

respectively, for one of the radiologists and 91, 97, 94, and 95 percent, respectively, for the second radiologist.

- In a second study of 158 patients suspected of small bowel neoplasms after negative upper and lower endoscopies, preoperative MR enteroclysis/enterography identified 31 of the 32 small bowel tumors (97 percent) with no false positive results [26]. The correct histology was predicted by MR enterography in only 62 percent of cases.

  The extrapolation of these results to the general population is limited by the small size and retrospective nature of the study, and the much higher prevalence of small bowel tumors in this highly select cohort.

**Integrated PET/CT** — Integrated positron emission tomography (PET)/CT scanning using the radiotracer 18-FDG, may be useful for the initial diagnosis of small bowel neoplasms, staging, evaluating response to treatment, and restaging at the time of suspected disease recurrence. Utility varies according to histology.

**Adenocarcinoma** — FDG PET/CT allows primary lesion detection of small bowel adenocarcinomas [27-29], although sensitivity compared with other imaging methods has not been systematically studied. The ability of PET/CT to detect local and distant metastatic disease has not been formally evaluated. However, it seems reasonable to extrapolate from the experience with colorectal adenocarcinoma, in which PET scanning is useful as an adjunct to other imaging modalities for localizing sites of disease recurrence in patients with a rising carcinoembryonic antigen (CEA) post-treatment and nondiagnostic conventional imaging, and for evaluation of patients who are thought to be candidates for resection of isolated colorectal cancer liver metastases, in whom the routine use of PET prior to attempted resection reduces the number of nontherapeutic laparotomies. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Positron emission tomography'.)

**Lymphoma** — FDG uptake is variable in the typical lymphomas that arise in the GI tract. Of the histologies most commonly seen in the small intestine, diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma, Burkitt lymphoma, and enteropathy associated T cell lymphoma are typically FDG-avid [30]. By contrast, marginal zone lymphoma and follicular lymphoma have variable FDG-avidity. Many clinicians incorporate PET into the pretreatment evaluation of patients with DLBCL of the GI tract, but its utility in other subtypes is controversial. This issue is addressed in more detail elsewhere. (See "Pretreatment evaluation and staging of non-Hodgkin lymphomas", section on 'Choice of imaging modality' and "Pretreatment evaluation and staging of non-Hodgkin lymphomas", section on 'Positron emission tomography (PET)'.)

**Sarcoma** — 18-FDG PET/CT is highly sensitive (86 to 100 percent) for detecting tumors with a high glucose metabolism, such as GI stromal tumors, and PET can be useful for detecting an unknown primary site or resolving ambiguities from CT (eg, when the CT findings are inconclusive or inconsistent with the clinical findings). However, because of limitations in specificity, PET has not replaced CT as the initial imaging modality of choice in patients suspected of having a GI tract mesenchymal tumor. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Imaging the primary tumor'.)

While a baseline PET may be indicated for patients in whom PET will be used to monitor the response to therapy with a tyrosine kinase inhibitor, nearly all the data obtained by PET scan imaging can be found in a good quality traditional IV-contrasted CT scan, with superior anatomic definition. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Assessing response to therapy' and "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Response assessment'.)

### Neuroendocrine tumors

**Cross-sectional imaging** — For NETs, an abdominal CT with oral contrast has a sensitivity of 77 to 87 percent for identifying at least one of the manifestations of these tumors [31-34]. This may be the primary tumor, mesenteric stranding due to tumor involvement and a fibrotic response ( image 1), liver metastases (which are invariably present when carcinoid syndrome arises from a gut primary), or a mesenteric mass reflecting lymph node enlargement. Gadolinium-enhanced MRI of the liver is more sensitive than abdominal CT for evaluating both the presence and extent of liver metastases in patients with a NET [34,35]. (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring".)

However, imaging, even with combinations of CT and MRI, tends to underestimate the extent of peritoneal, mesenteric, hepatic, and bony metastatic disease in patients with small bowel NETs [34]. Accurate staging might be best achieved at the time of laparotomy, or through the use of highly sensitive somatostatin receptor-based imaging (eg, Ga-68 DOTATATE PET/CT scanning).

**FDG-PET** — Well-differentiated NETs of the small bowel are relatively indolent and typically non-FDG avid, and therefore fluorodeoxyglucose (FDG)-positron emission tomography (PET) is of little utility. By contrast, FDG-PET scanning is indicated with high-grade neuroendocrine carcinomas, most (but not all) of which are poorly differentiated. (See "High-grade gastroenteropancreatic neuroendocrine neoplasms", section on 'Radiographic studies'.)

**Somatostatin receptor-based imaging** — Because somatostatin receptors are expressed by the majority of well-differentiated NETs, a number of unique diagnostic tests such as

somatostatin receptor-based imaging can be utilized to aid in the diagnosis. (See "Neuroendocrine neoplasms of unknown primary site", section on 'Initial workup' and "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Somatostatin receptor-based imaging techniques' and "Diagnosis of carcinoid syndrome and tumor localization", section on 'Tumor localization and staging'.)

Somatostatin-based tracers for functional PET imaging, including gallium Ga-68 DOTATATE (Ga-68 DOTATATE), gallium Ga-68 DOTATOC (Ga-68 DOTATOC), or copper Cu-64 DOTATATE (Cu-64 DOTATATE), are approved in the United States for use in conjunction with integrated PET/CT for diagnostic imaging of NETs. We suggest somatostatin receptor-based imaging for all patients with a small bowel NET, with the possible exception of a very small tumor that is completely resected. Guidelines from the North American Neuroendocrine Tumor Society (NANETS) and others state a preference for Ga-68 DOTATATE PET scanning over older methods of somatostatin receptor imaging (eg, 111-In pentetreotide SPECT imaging [Octreoscan]) for initial staging of small bowel NETs [36,37] given its greater sensitivity. (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Somatostatin receptor-based imaging techniques'.)

Somatostatin receptor-based imaging may be particularly helpful for tumor localization in the case of a metastatic NET of unknown primary site. This topic is discussed in detail elsewhere. (See "Neuroendocrine neoplasms of unknown primary site", section on 'Evaluation and management'.)

**Endoscopic techniques** — The advantages and disadvantages of several endoscopic methods for evaluation of the small bowel are outlined in the table ( table 2).

**Upper endoscopy/EUS** — Standard upper endoscopy (esophagogastroduodenoscopy [EGD]) is capable of reaching only the proximal duodenum. It may be adequate if a proximal small bowel tumor is suspected. For localized primary tumors of the duodenum, EGD with endoscopic ultrasound (EUS) may provide optimal tumor (T) and nodal (N) staging, especially in cases where neoadjuvant therapy is being contemplated prior to surgical resection. In addition for masses in the second portion of the duodenum, EUS may delineate the primary site of tumor origin in relation to the neighboring anatomic structures of the ampulla of Vater, distal common bile duct, and pancreas.

**Wireless video capsule endoscopy** — Wireless VCE provides a noninvasive means of visualizing the entire small bowel. It has become a standard diagnostic approach for patients with suspected small bowel bleeding (previously referred to as obscure GI bleeding) and has

been recommended as the appropriate first-line investigation in such patients [38]. Because of its capacity to visualize the small bowel mucosa directly, this technology has supplanted some of the older techniques, such as enteroclysis, in the workup of small bowel tumors. (See "Wireless video capsule endoscopy".)

The utility of VCE in diagnosing small bowel tumors was demonstrated in a retrospective study of 562 patients who underwent the procedure at Mount Sinai Medical Center from 2001 to 2003 [39]. Indications for endoscopy were suspected small bowel bleeding (79 percent), chronic abdominal pain (5 percent), or search for a well-differentiated NET primary (4 percent). A total of 50 patients were diagnosed with small bowel tumors, of which 48 percent were malignant. Among patients who were younger than 50 years old undergoing VCE for suspected small bowel bleeding, nine (13 percent) had a small bowel tumor. There was one false-positive result (which prompted a negative surgical exploration), but the number of false-negative studies could not be ascertained as information on outcomes among patients who had a negative VCE was not available.

Information on the false-negative rate of VCE was provided in a meta-analysis of 530 patients from 24 studies in which VCE was compared prospectively with a standard diagnostic workup (push enteroscopy in 300 patients, small-bowel series in 140 patients, or colonoscopy with ileoscopy in 90 patients) [40]. A total of 106 neoplasms were diagnosed, of which VCE missed 20 (false-negative rate 19 percent). However, this was lower than the miss rate for the standard diagnostic workup method (63 percent).

However, VCE may be less sensitive for detecting small bowel tumors than CT enterography. In a study that included 17 patients with small bowel tumors who underwent both CT enterography and capsule endoscopy, CT enterography was more sensitive than capsule endoscopy for detecting small bowel tumors (94 versus 35 percent) [18]. Lesions in the duodenum and proximal jejunum are easily missed because of the rapid transit of the capsule through these areas. (See "Wireless video capsule endoscopy", section on 'Small bowel tumors, polyps, and other pathology'.)

The main disadvantage of VCE is that it does not permit tissue sampling. It should not be performed in patients in whom small bowel obstruction is suspected since the capsule may become lodged proximal to the obstruction and may require enteroscopy or laparotomy for retrieval, as has been seen in 10 to 25 percent of patients with small bowel tumors in reported series [41]. (See "Wireless video capsule endoscopy", section on 'Capsule retention'.)

**Enteroscopy** — Enteroscopy refers to the passage of a colonoscope or special enteroscope beyond the ligament of Treitz using a push technique, or a device-assisted approach such as a

single balloon enteroscopy, double balloon enteroscopy or, less commonly, spiral enteroscopy technique. Enteroscopy may also be performed intraoperatively with surgical assistance [42]. The main advantage compared with wireless VCE is the ability to obtain tissue samples and perform therapeutic interventions. (See "Overview of deep small bowel enteroscopy".)

Enteroscopy is a valuable tool for the detection and diagnosis of small bowel tumors [43] and can be complementary to VCE by allowing for tissue sampling of lesions identified during VCE. However, the procedure is invasive, requires longer periods of provider time and patient sedation, can be technically challenging secondary to the nature of the procedure, is not reliably able to visualize the entire small bowel, and requires expertise and equipment which are not always available. Deep enteroscopy techniques are described in more detail elsewhere. (See "Evaluation of suspected small bowel bleeding (formerly obscure gastrointestinal bleeding)" and "Overview of deep small bowel enteroscopy".)

**Tumor markers** — There are no serum tumor markers that are sufficiently sensitive or specific to aid in the diagnose of any small bowel tumor.

**Small bowel adenocarcinoma** — The majority of small bowel adenocarcinomas are positive for CEA by immunohistochemistry [44,45], and serum CEA is elevated in 30 to 44 percent of patients with metastatic or locally advanced small bowel adenocarcinoma [46,47]. Approximately 41 to 63 percent of small bowel adenocarcinomas have elevated levels of carbohydrate antigen 19-9 (CA 19-9) [47,48]. However, neither CEA nor CA 19-9 is sufficiently sensitive nor specific to be used for diagnostic purposes, especially in patients with a localized tumor.

On the other hand, assay of CEA and/or CA 19-9 is appropriate for newly diagnosed patients with a small bowel adenocarcinoma because if elevated, levels should normalize after potentially curative resection, and that tumor marker can be followed serially to assess for disease recurrence and response to therapy. Updated guidelines for workup and staging of small bowel adenocarcinomas from the National Comprehensive Cancer Network (NCCN) recommend testing serum levels of CEA and CA 19-9 in all patients [49].

**Well-differentiated NETs** — Given the presence of somatostatin receptors and secretion of both nonhormonal and hormonal tumor markers ( table 3) by neuroendocrine tumors (NETs), a number of unique diagnostic tests including serum chromogranin A (CgA) and urinary 5-hydroxyindoleacetic acid (5-HIAA) have been utilized to aid in the diagnosis of a well-differentiated NET. However, the limitations of nonhormonal markers like CgA in terms of sensitivity and specificity ( table 4) has led to a de-emphasis of their use in patients with newly diagnosed localized NETs of the GI tract in many guidelines, including those of the NCCN [49]

and NANETS [50]. These markers should not be used as a diagnostic test for NETs or for post-treatment surveillance after surgical treatment of a nonmetastatic NET. Histopathologic evaluation of tissue by a dedicated pathologist remains the gold standard for the diagnosis of an NET.

On the other hand, for patients with chronic, unexplained diarrhea and/or cutaneous flushing, an elevated level of 5-HIAA (with appropriate dietary restrictions, ( table 5)) is suggestive of carcinoid syndrome and should lead to further diagnostic workup.

This subject is discussed in detail elsewhere. (See "Overview of tumor biomarkers in gastroenteropancreatic neuroendocrine tumors" and "Diagnosis of carcinoid syndrome and tumor localization", section on 'Biochemical testing for carcinoid syndrome'.)

**Surgical exploration** — Surgical exploration (diagnostic laparoscopy/exploratory laparotomy) is the most sensitive diagnostic modality in evaluating a patient with a high suspicion of having a small bowel neoplasm, and may be needed if the initial diagnostic evaluation is unrevealing.

In the past, despite a thorough history, physical examination, and complete diagnostic workup, the correct diagnosis of small bowel malignancy was established preoperatively in only 70 percent of cases, with the remainder diagnosed at laparotomy [51]. However, improvements in cross-sectional imaging and the development of techniques such as VCE has reduced the need for surgical exploration.

Nevertheless, exploration may be needed for a patient with occult GI bleeding, unexplained weight loss, or vague abdominal pain and an otherwise unrevealing diagnostic evaluation, as long as it is consistent with the goals of care. Laparoscopy may also be useful for establishing the diagnosis of malignancy when the workup is otherwise negative and for obtaining adequate tissue samples if a diagnosis of lymphoma is suspected. Surgical treatment of small bowel neoplasms is addressed in more detail elsewhere. (See "Treatment of small bowel neoplasms".)

## STAGING

Staging systems differ according to the primary histology.

- **Adenocarcinoma** – The most commonly used staging system for small bowel adenocarcinomas is the tumor, node, metastasis (TNM) system of the combined American Joint Committee on Cancer/Union for International Cancer Control. The most recent version (eighth edition, 2017) has some major changes compared with the earlier (seventh edition, 2010) classification, with revised definitions of T stage; redefined N1 disease, as

one or two positive nodes; and redefined N2 disease, as more than two positive nodes ( table 6) [52]. As with the prior version, the prognostic stage groupings are only for adenocarcinoma.

- **Lymphoma** – The Ann Arbor staging system developed in 1971 for Hodgkin lymphoma (HL) has been adapted (the Lugano classification) for staging non-Hodgkin lymphomas (NHLs) ( table 7). This staging system focuses on the number of tumor sites (nodal and extranodal) and location. The staging system used for lymphoma and the diagnostic/staging tests that are recommended for the evaluation of a patient with NHL are discussed in detail elsewhere. (See "Pretreatment evaluation and staging of non-Hodgkin lymphomas".)

- **Sarcoma** – Visceral leiomyosarcomas are staged according to the TNM system for soft tissue sarcomas. The most recent version (eighth edition, 2017) has a separate and unique TNM staging classification for soft tissue sarcomas arising in the abdominal and thoracic viscera, but there are no corresponding prognostic stage groupings ( table 8) [53]. A separate TNM staging system is in place for gastrointestinal stromal tumors ( table 9) [54]. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma" and "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Staging system'.)

- **Neuroendocrine tumors** – Separate TNM staging classifications are available for neuroendocrine tumors of the duodenum/ampulla ( table 10) [55] and for tumors arising in the jejunum and ileum ( table 11) [56]. (See "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Small intestine'.)

  Notably, accurate staging after surgery for a small bowel neuroendocrine tumor requires a minimum of eight lymph nodes to be examined [57]. (See "Treatment of small bowel neoplasms", section on 'Treatment of locoregional disease'.)

## HISTOLOGY AND DIFFERENTIAL DIAGNOSIS

Differentiating the various small bowel tumors on light microscopy is generally straightforward, and the results of immunohistochemical (IHC) and/or cytometric studies are usually confirmatory:

- The morphologic appearance of gastrointestinal stromal tumors (GISTs) can be predominantly spindle cell or epithelioid, and these tumors have a characteristic molecular

signature. IHC staining can help to distinguish GISTs from other subepithelial tumors that may arise in the GI tract ( table 12). The vast majority of GISTs (over 95 percent) express the CD117 antigen, in contrast to leiomyomas and other spindle-cell tumors of the GI tract (eg, leiomyosarcomas), which are typically CD117-negative.

The CD117 antigen, which can be identified by IHC, is part of the KIT transmembrane receptor tyrosine kinase, a product of the *c-kit* (also denoted as *KIT*) protooncogene. In more than 80 percent of GIST cases, a mutation in the *KIT* gene leads to a structural variant of the KIT protein, which is abnormally activated and enables oncogenic signaling in the cell.

A subset of KIT-negative GISTs have activating mutations in a different receptor tyrosine kinase, platelet-derived growth factor receptor-alpha, which can only be identified using molecular techniques. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Histopathology'.)

- Neuroendocrine differentiation, as is characteristic of a well-differentiated GI neuroendocrine tumor (carcinoid), can be demonstrated by IHC staining for synaptophysin or chromogranin. (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on 'Morphology and immunohistochemistry' and "Neuroendocrine neoplasms of unknown primary site", section on 'Pathologic classification'.)

- IHC or flow cytometric studies for cell surface antigens typically identify lymphomas as being of either B cell or T cell origin. (See "Clinical presentation and initial evaluation of non-Hodgkin lymphoma", section on 'Analysis of biopsy material'.)

- Differentiating an adenocarcinoma of the small bowel from other bowel adenocarcinomas (particularly in the setting of a locally advanced lesion) can be challenging. In contrast to colorectal cancers, which are almost always cytokeratin (CK) 20 positive and CK 7 negative, adenocarcinomas of the small bowel are less often CK 20 positive (47 to 67 percent) and more often CK7 positive (34 to 100 percent) [58,59]. Additional IHC staining with carcinoembryonic antigen, CDX2, and MUC1 may further be positive in 50 percent [44,45], 43 percent [60], and 38 percent of small bowel adenocarcinomas, respectively, to differentiate from other small intestinal histologies, though may not differentiate metastases from other GI primary sites of origin. (See "Pathology and prognostic determinants of colorectal cancer".)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Well-differentiated gastroenteropancreatic neuroendocrine tumors" and "Society guideline links: Lymphoma diagnosis and staging" and "Society guideline links: Bowel obstruction" and "Society guideline links: Gastrointestinal bleeding in adults" and "Society guideline links: Gastrointestinal stromal tumors" and "Society guideline links: Soft tissue sarcoma".)

## SUMMARY AND RECOMMENDATIONS

- **Clinical features**
  - A variety of tumors, both malignant and benign, may arise within the small intestine. Malignant tumors include adenocarcinomas, neuroendocrine tumors, stromal tumors (gastrointestinal stromal tumors [GISTs] and non-GIST soft tissue sarcomas), and lymphomas. Benign lesions that may arise in the small bowel include adenomas, leiomyomas, fibromas, and lipomas.
  - The diagnosis of a small bowel tumor is often made late in the course of the disease because of their rarity and the nonspecificity of symptoms (abdominal pain, weight loss, nausea and vomiting, occult GI tract bleeding). (See "Epidemiology, clinical features, and types of small bowel neoplasms", section on 'Clinical presentation'.)
- **Diagnostic evaluation** – Symptomatic patients and those with an incidental finding on cross-sectional imaging done for another reason in whom a small bowel tumor is part of the differential diagnosis should undergo a complete history, physical examination. A minimum laboratory workup should include a complete blood count with differential, measurement of serum electrolytes, fecal occult blood sampling, and liver function tests. (See 'Diagnostic evaluation' above.)
  - **Symptomatic patients** – There is no single method that is best for imaging of the small intestine in a symptomatic patient with a suspected small bowel tumor. The choices are radiographic (primarily CT scan) or endoscopic (wireless video capsule endoscopy [VCE], push enteroscopy, or device-assisted enteroscopy). (See 'Radiographic imaging' above.)

Multiple tests may be needed sequentially. The best testing strategy and sequence of diagnostic tests are not established, and there is debate as to how much diagnostic workup is adequate to exclude a small bowel tumor.

Our approach to symptomatic patients depends on the predominant symptom. (See 'Our approach to patients with specific symptoms' above.)

The presence of carcinoid syndrome should be considered when the patient has suggestive symptoms, such as otherwise unexplained diarrhea or flushing. In such cases, additional diagnostic testing may include biochemical tests such as a 24-hour urine collection for 5-hydroxyindoleacetic acid and somatostatin receptor-based imaging. (See 'Chronic diarrhea with or without cutaneous flushing' above.)

- **Incidental finding** – Our approach to patients with a suspected small bowel tumor because of an incidental finding on cross-sectional imaging done for another purpose is outlined in the algorithm ( algorithm 1), and summarized as follows (see 'Patients with incidental findings' above):

  - If imaging suggests a small intestinal mass and there is no evidence of metastatic disease, we recommend the appropriate endoscopic evaluation (esophagogastroduodenoscopy [EGD], push enteroscopy, ileocolonoscopy, or device-assisted enteroscopy depending on the location of the lesion) in order to visualize the mass and obtain tissue for pathologic diagnosis.

  - If endoscopic evaluation is complete and unremarkable, and if suspicion for invasive malignancy is low, we recommend close follow-up with short-interval (eg, three months) cross-sectional imaging.

  - If endoscopic evaluation is incomplete, and there is no evidence of obstruction, VCE is recommended for visualization of areas not accessed by endoscopy, although tissue cannot be sampled using this approach.

  - If suspicion is high for an invasive malignancy, options for further workup include CT enterography, integrated FDG-PET/CT, somatostatin receptor-based imaging, or referral for surgical evaluation.

- **Surgical exploration** – Surgical exploration (diagnostic laparoscopy/exploratory laparotomy/intraoperative enteroscopy) is the most sensitive diagnostic modality in evaluating a patient with a high suspicion of having a small bowel neoplasm, and may

be needed if the initial diagnostic evaluation is unrevealing. (See 'Surgical exploration' above.)

- **Tumor markers** – There are no serum tumor markers that are sufficiently sensitive or specific to aid in the diagnose of any small bowel tumor. (See 'Tumor markers' above.)

- **Staging and histologic diagnosis**
  - Staging systems for small bowel tumors differ according to the primary histology. (See 'Staging' above.)
  - Differentiating the various small bowel tumors on light microscopy is generally straightforward, and the results of immunohistochemical and/or cytometric studies are usually confirmatory. (See 'Histology and differential diagnosis' above.)

## ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges James C Cusack Jr, MD, who contributed to an earlier version of this topic review.



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Topic 2516 Version 39.0

## GRAPHICS

### Evaluation of suspected small bowel neoplasm identified as an incidental findi imaging


EGD: esophagogastroduodenoscopy; CT: computed tomography; FDG PET: fluorodeoxyglucose-positron em

* Additional imaging (eg, CT chest) may be needed to evaluate for additional sites of metastatic disease.

¶ EGD is typically able to examine through the second portion of the duodenum; push enteroscopy can adva jejunum. Because of its capacity to advance deeply into small bowel, device-assisted enteroscopy may be en

choice but success is variable, even in expert hands.

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Graphic 133178 Version 3.0

## Causes of bowel obstruction

| Lesion | Etiology | Risk factors |
|---|---|---|
| **Extrinsic lesions** | Adhesions | Prior surgery, diverticulitis, Crohn disease, VP shunt, peritonitis (eg, tuberculous peritonitis) |
| | Hernia (congenital, acquired) | Abdominal wall hernia, inguinal hernia, femoral hernia, diaphragmatic hernia |
| | Volvulus | Chronic constipation, congenital abnormal mesenteric attachments |
| | Intra-abdominal abscess | Diverticulitis, appendicitis, Crohn disease |
| | Peritoneal carcinomatosis | Ovarian cancer, colon cancer, gastric cancer |
| | Endometriosis | |
| | Sclerosing mesenteritis | Prior surgery, abdominal trauma, autoimmune disorders, malignancy, neuroendocrine tumor |
| | Desmoid tumor/other soft tissue sarcoma (rare) | |
| | Superior mesenteric artery syndrome | Rapid weight loss |
| **Intrinsic lesions** | Congenital malformations, atresia, duplication | Refer to appropriate topic reviews |
| | Large bowel neoplasm | |
| | Adenocarcinoma | Hereditary colorectal cancer syndromes (HNPCC, FAP), inflammatory bowel disease, bowel irradiation, others (refer to appropriate topic reviews) |
| | Desmoid | |
| | Carcinoid | |
| | Neuroendocrine tumor | |
| | Lymphoma | |
| | Small bowel neoplasm* | |
| | Adenocarcinoma | Hereditary cancer syndromes (HNPCC, FAP, Peutz-Jeghers, *MUTYH*-associated polyposis, attenuated FAP) |

| | | |
|---|---|---|
| | Leiomyosarcoma | |
| | Paraganglioma | |
| | Schwannoma | |
| | Metastatic disease | Melanoma, breast cancer, cervical cancer, colon cancer (refer to appropriate topic reviews) |
| | Gastrointestinal stromal tumor | |
| | Neuroendocrine tumor | |
| | Lymphoma | Chronic inflammation |
| | Benign lesions | Peutz-Jeghers polyps, xanthomatosis, leiomyoma |
| | Anastomotic stricture | Prior intestinal surgery |
| | Inflammatory stricture | Crohn disease, diverticular disease, NSAID enteropathy |
| | Ischemic stricture | Peripheral artery disease, aortic surgery, colon resection |
| | Radiation enteritis/stricture | Prior abdominal or pelvic irradiation |
| **Intraluminal obstruction of normal bowel** | Intussusception* | Small bowel tumor* |
| | Gallstones | Cholecystitis |
| | Congenital webs | |
| | Feces or meconium | Cystic fibrosis, severe constipation |
| | Bezoar (phytobezoar, pharmacobezoar) | Intestinal motility disorders |
| | Intramural hematoma | |
| | Traumatic | Blunt abdominal trauma |
| | Spontaneous | Antithrombotic therapy |
| | Foreign body | |
| | Ingested | Psychiatric disturbance |
| | Medical device migration | PEG tube, jejunal tube |
| | Parasites | *Ascaris lumbricoides*, *Strongyloides stercoralis* |

VP: ventriculoperitoneal; HNPCC: hereditary nonpolyposis colorectal cancer; FAP: familial adenomatous polyposis; NSAID: nonsteroidal anti-inflammatory drug; PEG: percutaneous endoscopic gastrostomy.

* May be due to an intrinsic lesion serving as a lead point.

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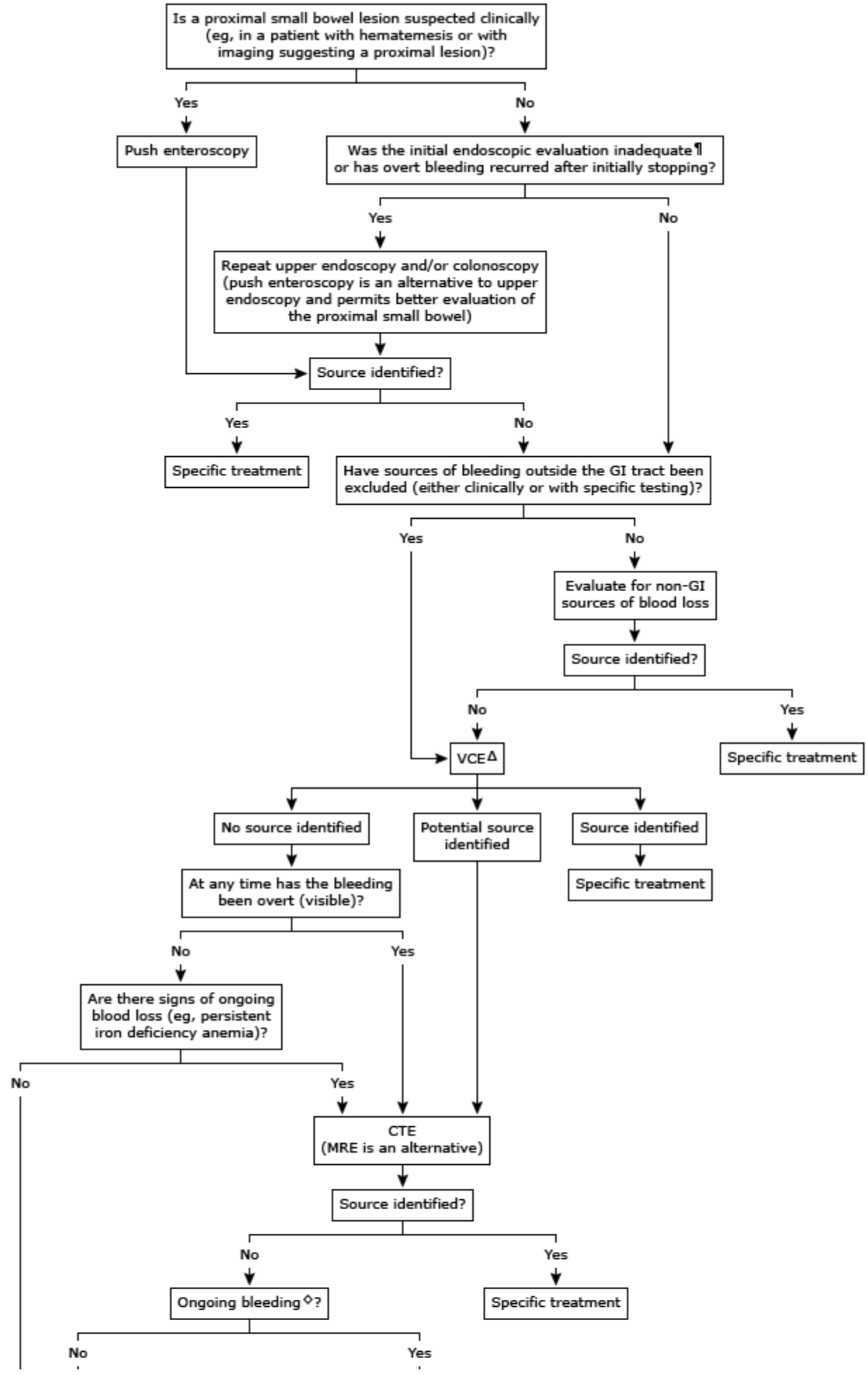
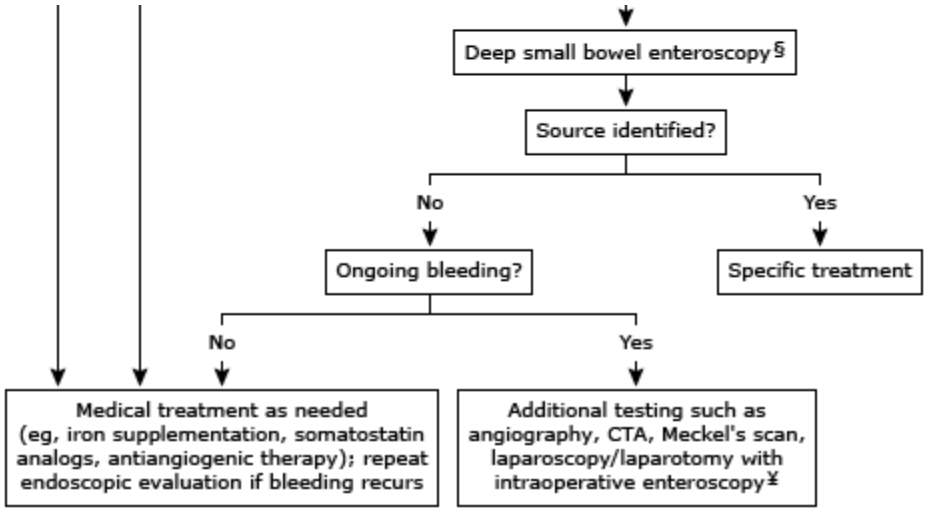
Graphic 53183 Version 8.0

## Evaluation of suspected small bowel bleeding in hemodynamically stable patients*


Is a proximal small bowel lesion suspected clinically (eg, in a patient with hematemesis or with imaging suggesting a proximal lesion)?
Yes
No
Push enteroscopy
Was the initial endoscopic evaluation inadequate¶ or has overt bleeding recurred after initially stopping?
Yes
No
Repeat upper endoscopy and/or colonoscopy (push enteroscopy is an alternative to upper endoscopy and permits better evaluation of the proximal small bowel)
Source identified?
Yes
No
Specific treatment
Have sources of bleeding outside the GI tract been excluded (either clinically or with specific testing)?
Yes
No
Evaluate for non-GI sources of blood loss
Source identified?
No
Yes
Specific treatment
VCEΔ
No source identified
Potential source identified
Source identified
Specific treatment
At any time has the bleeding been overt (visible)?
No
Yes
Are there signs of ongoing blood loss (eg, persistent iron deficiency anemia)?
No
Yes
CTE (MRE is an alternative)
Source identified?
No
Yes
Ongoing bleeding◇?
Specific treatment
No
Yes




GI: gastrointestinal; VCE: video capsule endoscopy; CTE: computed tomographic enterography; MRE: magnetic resonance enterography; CTA: computed tomographic angiography.

* Small bowel bleeding should be suspected in patients with signs of GI bleeding who have had a negative initial endoscopic evaluation (typically upper endoscopy and colonoscopy). The evaluation of hemodynamically unstable patients is discussed in the context of the specific bleeding manifestations (eg, hematemesis). Refer to UpToDate topic reviews on the evaluation and management of GI bleeding for details.

¶ For patients with risk factors for hemobilia or hemosuccus pancreaticus, the upper endoscopy should have included evaluation with a side-viewing duodenoscope. Patients with risk factors for an aortoenteric fistula should also have undergone CTA. If the initial upper endoscopy and/or colonoscopy was inadequate (eg, fair or poor visualization, failure to reach the cecum), repeat examination should be considered before initiating an evaluation for small bowel bleeding.

Δ VCE should be done as close to the acute bleeding episode as possible to increase diagnostic yield. Patients at risk for capsule retention should undergo small bowel imaging (eg, CTE) or a patency capsule study prior to VCE.

◇ In patients with significant comorbid illnesses with slow rates of blood loss, it may be reasonable to stop the evaluation and treat with iron repletion and/or transfusions as needed.

§ Push enteroscopy is an alternative if not already done and if deep small bowel enteroscopy is not available. Intraoperative enteroscopy is an alternative if there are contraindications to deep small bowel enteroscopy, such as dense intra-abdominal adhesions.

¥ The choice of test will depend on the rate of bleeding, patient characteristics, and the degree of suspicion for a small bowel lesion. A Meckel's scan should be performed in younger patients with overt bleeding. Angiography or CTA can be obtained if there is active bleeding. Surgical exploration is appropriate if no other studies have revealed a source and significant bleeding continues or if there is high suspicion for a small bowel neoplasm. If the evaluation is still negative, non-GI sources of blood loss should be reconsidered.

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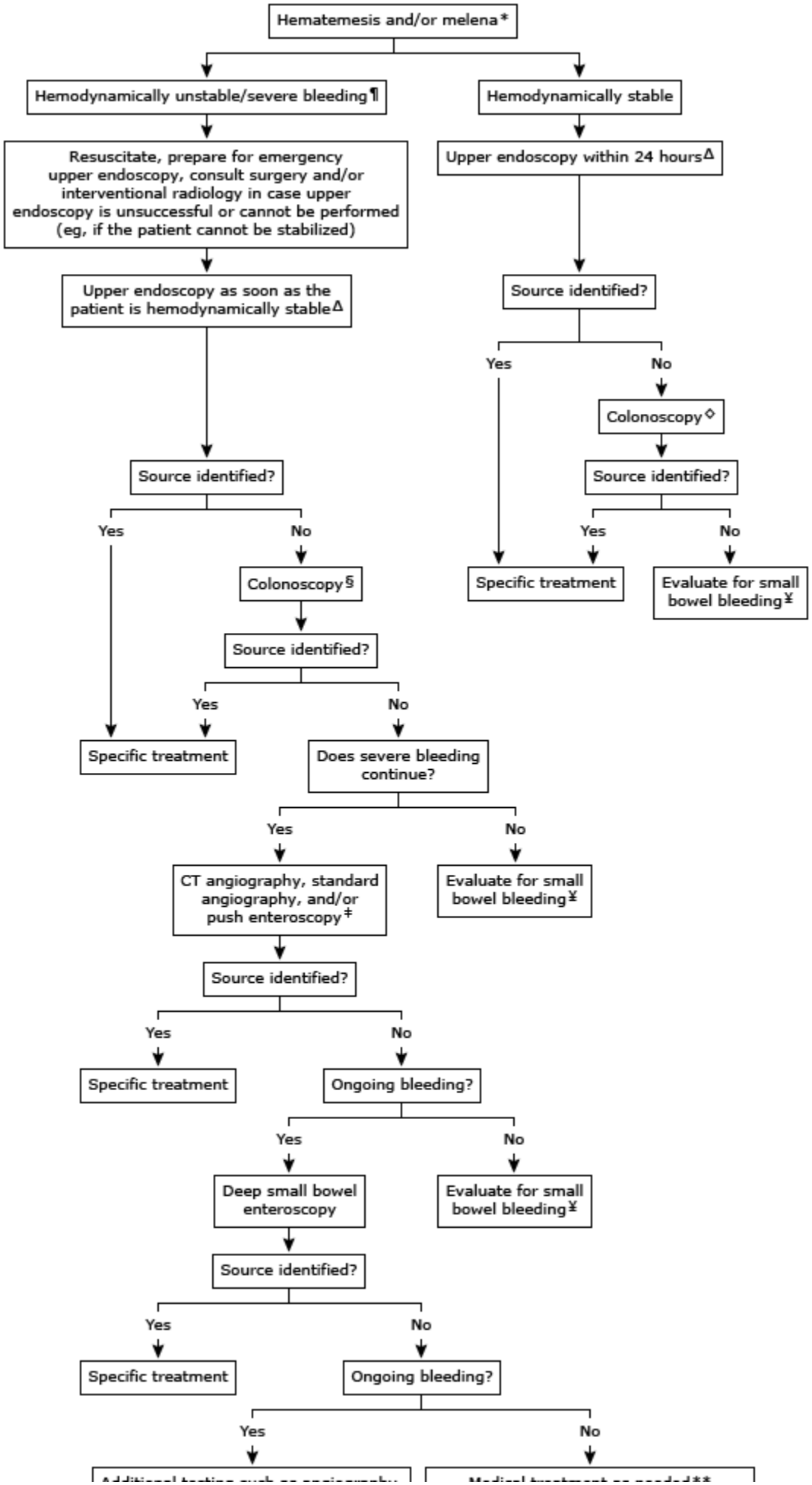
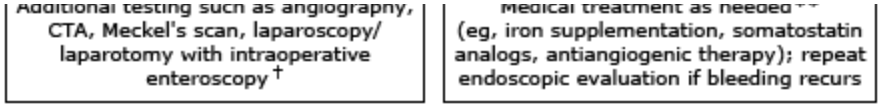
Graphic 95608 Version 4.0

## Evaluation of suspected upper gastrointestinal bleeding


Hematemesis and/or melena*
Hemodynamically unstable/severe bleeding¶
Hemodynamically stable
Resuscitate, prepare for emergency upper endoscopy, consult surgery and/or interventional radiology in case upper endoscopy is unsuccessful or cannot be performed (eg, if the patient cannot be stabilized)
Upper endoscopy within 24 hours△
Upper endoscopy as soon as the patient is hemodynamically stable△
Source identified?
Yes
No
Colonoscopy◇
Source identified?
Yes
No
Specific treatment
Evaluate for small bowel bleeding¥
Source identified?
Yes
No
Colonoscopy§
Source identified?
Yes
No
Specific treatment
Does severe bleeding continue?
Yes
No
CT angiography, standard angiography, and/or push enteroscopy‡
Evaluate for small bowel bleeding¥
Source identified?
Yes
No
Specific treatment
Ongoing bleeding?
Yes
No
Deep small bowel enteroscopy
Evaluate for small bowel bleeding¥
Source identified?
Yes
No
Specific treatment
Ongoing bleeding?
Yes
No




GI: gastrointestinal; CT: computed tomographic; CTA: computed tomographic angiography; MR: magnetic resonance.

* The presence of both hematemesis and melena suggests that brisk bleeding is present.

¶ Bleeding associated with signs such as hypotension, tachycardia, or orthostatic hypotension.

Δ Consider evaluation with a side-viewing duodenoscope if there are risk factors for hemobilia or hemosuccus pancreaticus; consider CTA (followed by push enteroscopy if the CTA is negative) in patients at risk for an aortoenteric fistula. Conventional angiography is typically performed if the patient remains hemodynamically unstable despite attempts at resuscitation.

◇ Patients who present with hematemesis do not need to undergo colonoscopy, since hematemesis suggests the bleeding is proximal to the ligament of Treitz. They should proceed directly to an evaluation for small bowel bleeding if upper endoscopy is negative. Colonoscopy is the next step in the evaluation of patients with melena.

§ If the patient becomes hemodynamically unstable following initial resuscitation, conventional angiography can be performed. Patients who present with hematemesis do not need to undergo colonoscopy and can skip this step in the evaluation because hematemesis suggests the bleeding is proximal to the ligament of Treitz.

¥ If the initial endoscopic evaluation was inadequate (eg, fair or poor visualization, failure to reach the cecum), repeat examination should be considered before initiating an evaluation for small bowel bleeding. Refer to UpToDate topic review on suspected small bowel bleeding for details.

‡ If not already done. If the patient remains hemodynamically stable and does not have evidence of aggressive bleeding (eg, ongoing hematochezia), perform a CTA or push enteroscopy (CTA is the initial test of choice if there is concern for an aortoenteric fistula). If the patient becomes hemodynamically unstable following initial resuscitation or has signs of aggressive bleeding, perform conventional angiography.

† If not already done, angiography or CTA may be obtained. If angiography or CTA has been performed and no source is identified, a Meckel's scan should be obtained in younger patients with overt bleeding, unless the only manifestation of bleeding was hematemesis. Surgical exploration is appropriate if no other studies have revealed a source and significant bleeding continues or if there is high suspicion for a small bowel neoplasm.

** If the deep small bowel enteroscopy was incomplete, a video capsule endoscopy study should be obtained, followed by CT enterography or MR enterography if the

capsule endoscopy is negative.

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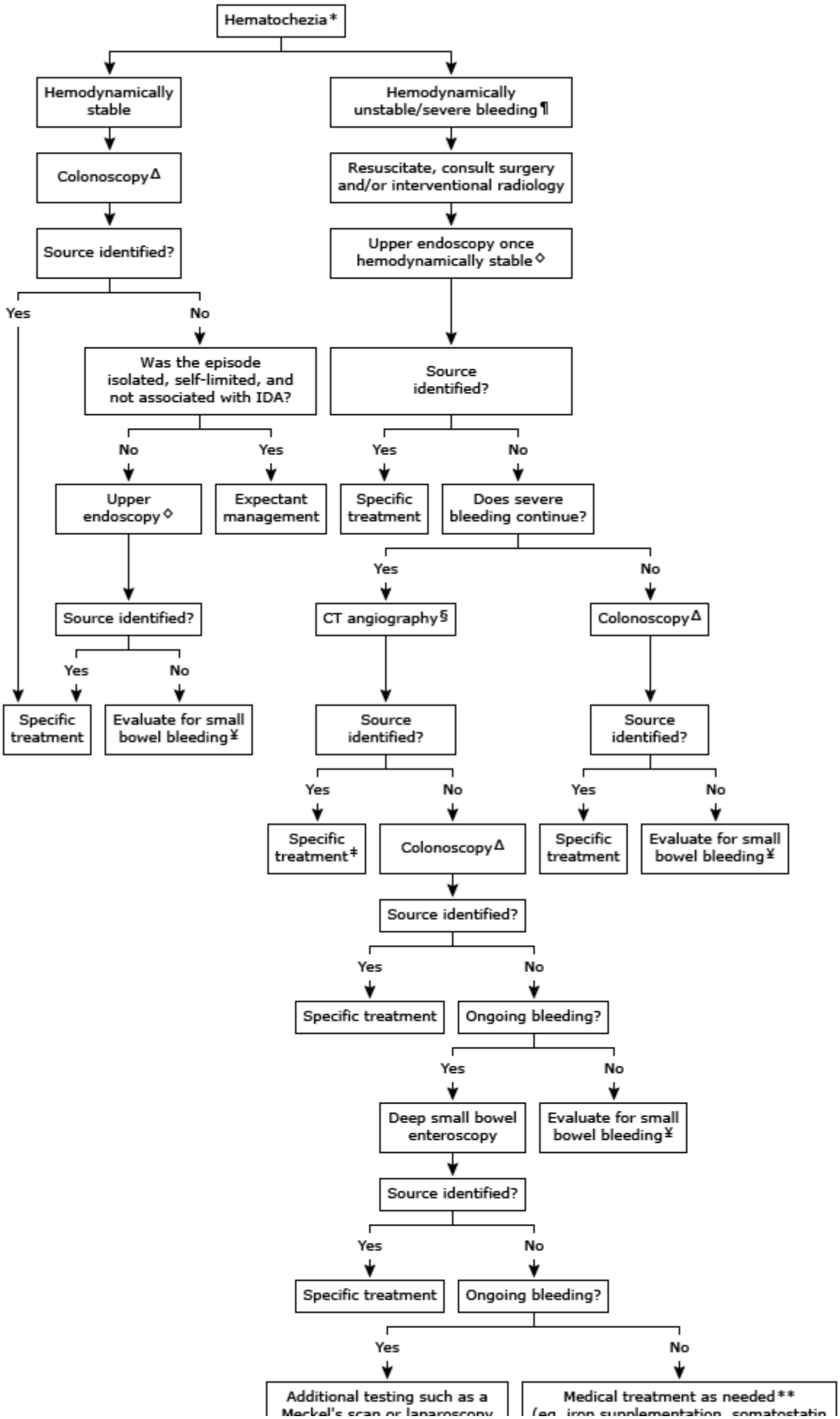
Graphic 105093 Version 4.0

## Evaluation of patients presenting with hematochezia (excluding those with minimal rectal bleeding)


Hematochezia*
Hemodynamically stable
Hemodynamically unstable/severe bleeding¶
Colonoscopy△
Resuscitate, consult surgery and/or interventional radiology
Source identified?
Upper endoscopy once hemodynamically stable◇
Yes
No
Was the episode isolated, self-limited, and not associated with IDA?
Source identified?
No
Yes
Yes
No
Upper endoscopy◇
Expectant management
Specific treatment
Does severe bleeding continue?
Source identified?
Yes
No
CT angiography§
Colonoscopy△
Yes
No
Specific treatment
Evaluate for small bowel bleeding¥
Source identified?
Source identified?
Yes
No
Yes
No
Specific treatment‡
Colonoscopy△
Specific treatment
Evaluate for small bowel bleeding¥
Source identified?
Yes
No
Specific treatment
Ongoing bleeding?
Yes
No
Deep small bowel enteroscopy
Evaluate for small bowel bleeding¥
Source identified?
Yes
No
Specific treatment
Ongoing bleeding?
Yes
No
Additional testing such as a
Medical treatment as needed**

| | |
|---|---|
| laparotomy with intraoperative enteroscopy † | analogs, antiangiogenic therapy); repeat endoscopic evaluation if bleeding recurs |

IDA: iron deficiency anemia; CTA: computed tomographic angiography; CT: computed tomographic; GI: gastrointestinal; MR: magnetic resonance.

* If hematemesis or melena is present the patient should be evaluated for upper GI bleeding. Refer to UpToDate topics on the evaluation of upper GI bleeding for details.

¶ Bleeding associated with signs such as hypotension, tachycardia, or orthostatic hypotension.

Δ Colonoscopy should be performed once the patient has been resuscitated and an adequate bowel preparation has been given (typically 4 to 6 L of polyethylene glycol). If the initial colonoscopy was inadequate (eg, inadequate visualization, failure to reach the cecum), repeat colonoscopy should be considered.

◇ Consider evaluation with a side-viewing duodenoscope in patients with risk factors for hemobilia or hemosuccus pancreaticus or CT angiography (followed by push enteroscopy if the CT angiography is negative) in patients at risk for an aortoenteric fistula. Conventional transvenous angiography is typically performed if the patient remains hemodynamically unstable despite attempts at resuscitation. If the suspicion for an upper GI source is moderate (rather than high), nasogastric lavage can be performed to look for evidence to support an upper GI source. Refer to UpToDate topics on lower GI bleeding in adults for additional details.

§ Positive CT angiography should be promptly referred for transcatheter angiography and embolization.

¥ Refer to UpToDate topic review on suspected small bowel bleeding for details.

‡ Following successful angiography, an elective colonoscopy may still need to be performed to evaluate the underlying cause of bleeding (eg, large colorectal polyp or neoplasia).

† A Meckel's scan should be performed in younger patients with overt bleeding. Surgical exploration is appropriate if no other studies have revealed a source and significant bleeding continues or if there is high suspicion for a small bowel neoplasm.

** If the deep small bowel enteroscopy was incomplete, a video capsule endoscopy study should be obtained, followed by CT or MR enterography if the capsule endoscopy is negative.

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Graphic 95345 Version 8.0

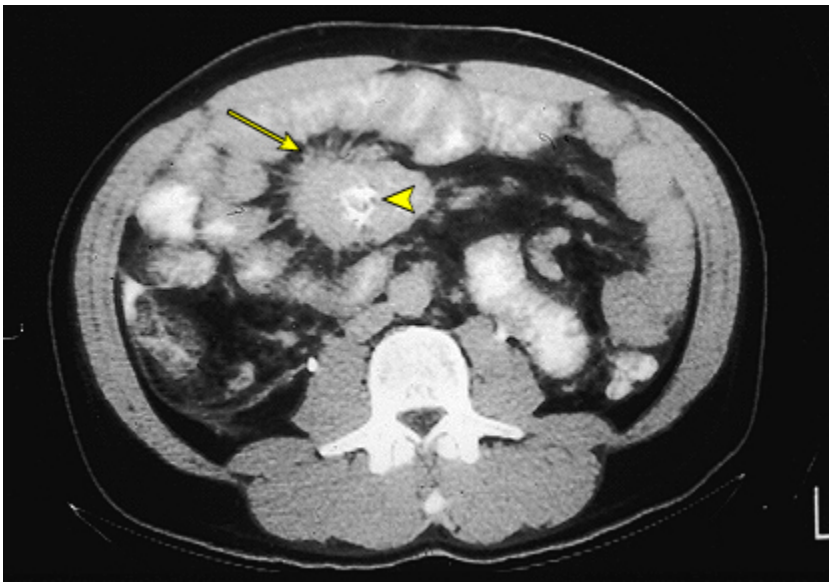
## Comparison of diagnostic tests used in the evaluation of suspected small bowel tumors

| Diagnostic test | Advantages | Disadvantages |
|---|---|---|
| Plain abdominal film | May show obstruction | Nonspecific |
| Upper gastrointestinal series/small bowel follow through | May show mass lesion, mucosal defect, or intussusception | No visualization outside lumen; not helpful in staging |
| CT scan, including CT enterography | Allows staging (extraluminal findings); may aid in diagnosis of tumor type | Inferior to direct visualization for assessment of the bowel lumen |
| MR enterography | Same as CT enterography, except limits exposure to medical radiation | Inferior to direct visualization for assessment of the bowel lumen |
| Upper endoscopy | Direct visualization of mucosal surface of duodenum; allows for biopsy; polypectomy possible | Invasive; limited to duodenum |
| Push enteroscopy | Extends visualization into proximal jejunum; allows for biopsy | Invasive; does not permit visualization of the entire small bowel (no visualization beyond proximal jejunum) |
| Double-balloon enteroscopy | Allows visualization of entire small bowel with capacity for biopsy and therapeutic intervention | Invasive; not widely available; small risk of pancreatitis; latex composition of balloons |
| Single-balloon enteroscopy | Same as double-balloon enteroscopy; more widely available | Lower total enteroscopy rate; more limited depth of insertion |
| Spiral enteroscopy | Same as single-balloon enteroscopy | Limited availability |
| Wireless video capsule endoscopy | Noninvasive | Does not permit tissue sampling; should not be performed if small bowel obstruction suspected |

CT: computed tomography.

Graphic 62087 Version 5.0

## Radiographic features associated with small bowel neuroendocrine tumors



Computed tomography (CT) scan demonstrates a soft tissue mass containing coarse central calcifications (arrowhead) in the right lower quadrant. This neuroendocrine tumor is producing a characteristic desmoplastic response with spiculation of the adjacent mesenteric fat (arrow).

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*Courtesy of Jonathan Kruskal, MD, PhD.*

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Graphic 78186 Version 5.0

## Products of well-differentiated neuroendocrine tumors

| **Amines** |
| --- |
| Serotonin |
| 5-Hydroxytryptophan |
| Norepinephrine |
| Dopamine |
| Histamine |
| **Polypeptides** |
| Kallikrein |
| Pancreatic polypeptide |
| Bradykinin |
| Motilin |
| Somatostatin |
| Vasoactive intestinal peptide |
| Neuropeptide K |
| Substance P |
| Neurokinin A |
| Neurokinin B |
| Corticotropin (ACTH) |
| Gastrin |
| Growth hormone |
| Peptide YY |
| Glucagon |
| Beta-endorphin |
| Neurotensin |
| Chromogranin A |
| **Prostaglandins** |

Graphic 79329 Version 2.0

## Conditions associated with elevated chromogranin A

| |
|---|
| **Gastroenteropancreatic NETs** |
| Gastrointestinal tract (carcinoid tumors) |
| Pancreatic NETs (islet cell tumors*) |
| **Endocrine disease** |
| Hyperparathyroidism |
| Hyperthyroidism |
| Pheochromocytoma |
| Pituitary tumors |
| Medullary thyroid carcinoma |
| **Gastrointestinal disorders** |
| Chronic atrophic gastritis |
| Chronic hepatitis |
| Colon cancer |
| Hepatocellular carcinoma |
| Inflammatory bowel disease |
| Irritable bowel syndrome |
| Liver cirrhosis |
| Pancreatic adenocarcinoma |
| Pancreatitis |
| **Cardiovascular disease** |
| Acute coronary syndrome |
| Arterial hypertension |
| Cardiac insufficiency/failure |
| Essential hypertension |
| Giant cell arteritis |
| **Drugs** |
| Proton pump inhibitors |
| Histamine-2 receptor antagonists |
| **Inflammatory disease** |

| |
|---|
| Airway obstruction in smokers |
| Chronic bronchitis |
| Systemic rheumatoid arthritis |
| Systemic inflammatory response syndrome |
| **Renal disorders** |
| Renal insufficiency/failure |
| **Non-gastrointestinal cancers** |
| Breast cancer |
| Ovarian cancer |
| Prostate cancer¶ |
| Small cell lung cancer |
| Neuroblastoma |

NETs: neuroendocrine tumors.

* eg, gastrinomas, VIPomas, somatostatinomas, glucagonomas, nonfunctioning pancreatic NETs.

¶ Even with a normal prostate-specific antigen (PSA) level.

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*Adapted from: Modlin IM, Gustafsson BI, Moss SF, et al. Chromogranin A--biological function and clinical utility in neuro endocrine tumor disease. Ann Surg Oncol 2010; 17:2427.*

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Graphic 73287 Version 7.0

## Substances that interfere with determination of urinary 5-HIAA

| **Falsely high values** |
| --- |
| Tryptophan-rich foods: avocados, pineapples, bananas, kiwi fruit, plums, eggplants, walnuts, hickory nuts, pecans, tomatoes, plantains, butternut squash |
| Drugs: acetaminophen, coumaric acid, guaifenesin, mephenesin, phenobarbital, reserpine, acetanilid, ephedrine, methamphetamine, nicotine, phentolamine, phenmetrazine, caffeine, fluorouracil, melphalan, methocarbamol, phenacetin, mesalamine |
| **Falsely low values** |
| Drugs: corticotrophin, ethanol, imipramine, levodopa, MAO inhibitors, phenothiazines, aspirin, isoniazid, gentisic acid, methenamine, streptozotocin, heparin, methyldopa |

5-HIAA: 5-hydroxyindoleacetic acid; MAO: monoamine oxidase.

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*Reference:*

1. *Corcuff J, Chardon L, El Hajji Ridah I, Brossaud J. Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. Endocr Connect 2017; 6:R87.*

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Graphic 79968 Version 7.0

## Small intestine adenocarcinoma TNM staging AJCC UICC 8th edition

| **Primary tumor (T)** | |
|---|---|
| **T category** | **T criteria** |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | High-grade dysplasia/carcinoma *in situ* |
| T1 | Tumor invades the lamina propria or submucosa |
| T1a | Tumor invades the lamina propria |
| T1b | Tumor invades the submucosa |
| T2 | Tumor invades the muscularis propria |
| T3 | Tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration* |
| T4 | Tumor perforates the visceral peritoneum or directly invades other organs or structures (eg, other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct) |
| * For T3 tumors, the nonperitonealized perimuscular tissue is, for the jejunum and ileum, part of the mesentery and, for the duodenum in areas where serosa is lacking, part of the interface with the pancreas. | |
| **Regional lymph nodes (N)** | |
| **N category** | **N criteria** |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in one or two regional lymph nodes |
| N2 | Metastasis in three or more regional lymph nodes |
| **Distant metastasis (M)** | |
| **M category** | **M criteria** |
| M0 | No distant metastasis |
| M1 | Distant metastasis present |
| **Prognostic stage groups** | |
| **Adenocarcinoma** | |

| When T is... | And N is... | And M is... | Then the stage group is... |
|---|---|---|---|
| Tis | N0 | M0 | 0 |
| T1-2 | N0 | M0 | I |
| T3 | N0 | M0 | IIA |
| T4 | N0 | M0 | IIB |
| Any T | N1 | M0 | IIIA |
| Any T | N2 | M0 | IIIB |
| Any T | Any N | M1 | IV |

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 110785 Version 9.0

## Revised staging system for primary nodal lymphomas (Lugano classification)

| Stage | Involvement | Extranodal status |
|---|---|---|
| **Limited** | | |
| I | One node or a group of adjacent nodes | Single extranodal lesions without nodal involvement |
| II | Two or more nodal groups on the same side of the diaphragm | Stage I or II by nodal extent with limited contiguous extranodal involvement |
| II bulky* | II as above with "bulky" disease | Not applicable |
| **Advanced** | | |
| III | Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement | Not applicable |
| IV | Additional noncontiguous extralymphatic involvement | Not applicable |

Extent of disease is determined by positron emission tomography/computed tomography (PET/CT) for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

* Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

*From: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014; 32(27):3059-67. Reprinted with permission.* 

Graphic 97479 Version 6.0

## Soft tissue sarcomas arising in the abdominal and thoracic viscera TNM staging AJCC UICC 8th edition*

| **Primary tumor (T)** | |
|---|---|
| **T category** | **T criteria** |
| TX | Primary tumor cannot be assessed |
| T1 | Organ confined |
| T2 | Tumor extension into tissue beyond organ |
| T2a | Invades serosa or visceral peritoneum |
| T2b | Extension beyond serosa (mesentery) |
| T3 | Invades another organ |
| T4 | Multifocal involvement |
| T4a | Multifocal (two sites) |
| T4b | Multifocal (three to five sites) |
| T4c | Multifocal (>5 sites) |
| **Regional lymph nodes (N)** | |
| **N category** | **N criteria** |
| N0 | No lymph node involvement or unknown lymph node status |
| N1 | Lymph node involvement present |
| **Distant metastasis (M)** | |
| **M category** | **M criteria** |
| M0 | No metastases |
| M1 | Metastases present |

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

* There is no recommended prognostic stage grouping at this time.

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Graphic 110739 Version 9.0

## GIST TNM staging AJCC UICC 8th edition

| **Primary tumor (T)** | |
|---|---|
| **T category** | **T criteria** |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor 2 cm or less |
| T2 | Tumor more than 2 cm but not more than 5 cm |
| T3 | Tumor more than 5 cm but not more than 10 cm |
| T4 | Tumor more than 10 cm in greatest dimension |
| **Regional lymph nodes (N)** | |
| **N category** | **N criteria** |
| N0 | No regional lymph node metastasis or unknown lymph node status |
| N1 | Regional lymph node metastasis |
| **Distant metastasis (M)** | |
| **M category** | **M criteria** |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| **Mitotic rate** | |
| **Mitotic rate** | **Definition** |
| Low | Five or fewer mitoses per 5 $mm^2$ |
| High | Over five mitoses per 5 $mm^2$ |
| **Prognostic stage groups** | |
| **Gastric and omental GIST** | |

| When T is… | And N is… | And M is… | And mitotic rate is… | Then the stage group is… |
|---|---|---|---|---|
| T1 or T2 | N0 | M0 | Low | IA |
| T3 | N0 | M0 | Low | IB |
| T1 | N0 | M0 | High | II |
| T2 | N0 | M0 | High | II |
| T4 | N0 | M0 | Low | II |

| | | | | |
|---|---|---|---|---|
| T3 | N0 | M0 | High | IIIA |
| T4 | N0 | M0 | High | IIIB |
| Any T | N1 | M0 | Any rate | IV |
| Any T | Any N | M1 | Any rate | IV |

| **Small intestinal, esophageal, colorectal, mesenteric, and peritoneal GIST** | | | | |
|---|---|---|---|---|
| **When T is…** | **And N is…** | **And M is…** | **And mitotic rate is…** | **Then the stage group is…** |
| T1 or T2 | N0 | M0 | Low | I |
| T3 | N0 | M0 | Low | II |
| T1 | N0 | M0 | High | IIIA |
| T4 | N0 | M0 | Low | IIIA |
| T2 | N0 | M0 | High | IIIB |
| T3 | N0 | M0 | High | IIIB |
| T4 | N0 | M0 | High | IIIB |
| Any T | N1 | M0 | Any rate | IV |
| Any T | Any N | M1 | Any rate | IV |

GIST: gastrointestinal stromal tumor; TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 110847 Version 8.0

## Neuroendocrine tumors of the duodenum and ampulla of Vater TNM staging AJCC UICC 8th edition

| **Primary tumor (T)** | |
|---|---|
| **T category** | **T criteria** |
| TX | Primary tumor cannot be assessed |
| T1 | Tumor invades the mucosa or submucosa only and is ≤1 cm (duodenal tumors).<br>Tumor ≤1 cm and confined within the sphincter of Oddi (ampullary tumors). |
| T2 | Tumor invades the muscularis propria or is >1 cm (duodenal).<br>Tumor invades through sphincter into duodenal submucosa or muscularis propria, or is >1 cm (ampullary). |
| T3 | Tumor invades the pancreas or peripancreatic adipose tissue |
| T4 | Tumor invades the visceral peritoneum (serosa) or other organs |
| *NOTE:* Multiple tumors should be designated as such (and the largest tumor should be used to assign the T category):<br>▪ If the number of tumors is known, use T(#); eg, pT3(4) N0 M0.<br>▪ If the number of tumors is unavailable or too numerous, use the m suffix, T(m); eg, pT3(m) N0 M0. | |
| **Regional lymph nodes (N)** | |
| **N category** | **N criteria** |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node involvement |
| N1 | Regional lymph node involvement |
| **Distant metastasis (M)** | |
| **M category** | **M criteria** |
| M0 | No distant metastasis |
| M1 | Distant metastases |
| M1a | Metastasis confined to liver |
| M1b | Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone) |
| M1c | Both hepatic and extrahepatic metastases |
| **Prognostic stage groups** | |

| When T is... | And N is... | And M is... | Then the stage group is... |
|---|---|---|---|
| T1 | N0 | M0 | I |
| T2 | N0 | M0 | II |
| T3 | N0 | M0 | II |
| T4 | N0 | M0 | III |
| Any T | N1 | M0 | III |
| Any T | Any N | M1 | IV |

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 111095 Version 8.0

## Neuroendocrine tumors of the jejunum and ileum TNM staging AJCC UICC 8th edition

| **Primary tumor (T)** | |
|---|---|
| **T category** | **T criteria** |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1* | Invades lamina propria or submucosa and less than or equal to 1 cm in size |
| T2* | Invades muscularis propria or greater than 1 cm in size |
| T3* | Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa |
| T4* | Invades visceral peritoneum (serosal) or other organs or adjacent structures |
| * *NOTE:* For any T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1 to 4, and # = number of primary tumors identified¶]; for multiple tumors with different T, use the highest.<br>¶ *Example:* If there are two primary tumors, only one of which invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal), we define the primary tumor as either T3(2) or T3(m). | |
| **Regional lymph nodes (N)** | |
| **N category** | **N criteria** |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis has occurred |
| N1 | Regional lymph node metastasis less than 12 nodes |
| N2 | Large mesenteric masses (>2 cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels |
| **Distant metastasis (M)** | |
| **M category** | **M criteria** |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Metastasis confined to liver |
| M1b | Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone) |
| M1c | Both hepatic and extrahepatic metastases |
| **Prognostic stage groups** | |

| When T is... | And N is... | And M is... | Then the stage group is... |
|---|---|---|---|
| TX, T0 | NX, N0, N1, N2 | M1 | IV |
| T1 | N0 | M0 | I |
| T1 | N1, N2 | M0 | III |
| T1 | NX, N0, N1, N2 | M1 | IV |
| T2 | N0 | M0 | II |
| T2 | N1, N2 | M0 | III |
| T2 | NX, N0, N1, N2 | M1 | IV |
| T3 | N0 | M0 | II |
| T3 | N1, N2 | M0 | III |
| T3 | NX, N0, N1, N2 | M1 | IV |
| T4 | N0 | M0 | III |
| T4 | N1, N2 | M0 | III |
| T4 | NX, N0, N1, N2 | M1 | IV |
| For multiple synchronous tumors, the highest T category should be used and the multiplicity or the number of tumors should be indicated in parenthesis: eg, T3(2) or T3(m). | | | |

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 111096 Version 9.0

## Immunohistochemical schema for the differential diagnosis of spindle cell tumors of the gastrointestinal tract

| Type | CD117 | DOG-1 | PKC-theta | CD34 | SMA* | S100 protein | Desmin |
|---|---|---|---|---|---|---|---|
| GISTs | + (>95%) | + (97%) | + (72%) | + (60 to 70%) | +/– (30 to 40%) | – (5% +) | Very rare |
| Leiomyoma | – | – | | + (10 to 15%) | + | – | + |
| Leiomyosarcoma | – | – | + (10%) | – | + | – | + |
| Schwannoma | – | – | + (10%) | – | – | + | – |

DOG-1: discovered on GIST-1; PKC-theta: protein kinase C theta; GISTs: gastrointestinal stromal tumors.

* Alpha smooth muscle actin.

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*Adapted from:*


1. *Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Int J Surg Pathol 2002; 10:81.*
2. *Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol 2000; 10:1134.*
3. *Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009; 33:1401.*
4. *Duensing A, Joseph NE, Medeiros F, et al. Protein Kinase C theta (PKCtheta) expression and constitutive activation in gastrointestinal stromal tumors (GISTs). Cancer Res 2004; 64:5127.*


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Graphic 79128 Version 5.0

## Contributor Disclosures

**Michael J Overman, MD** Grant/Research/Clinical Trial Support: BMS [Colon cancer]; Lilly [Small bowel adenocarcinoma]; Medimmune [Colon and pancreas cancer]; Merck [Colon cancer and MSI-high cancers]; Nouscom [Colon and gastric cancers]; Roche [MSI-high colon cancer]; Takeda [MSI-high cancers]. Consultant/Advisory Boards: 3D Medicines [Tumor-agnostic and MSI-high cancers]; AgilVax [Colon cancer]; BMS [Colon cancer]; Gilead Sciences [Colon cancer]; GlasxoSmithKline [Colon cancer]; Gritstone [Colon cancer]; Ipsen Biopharmaceuticals [Colon cancer]; Janssen research [Colon cancer]; Medimmune [Colon and pancreas cancer]; Merck [Colon cancer]; Novartis [Colon cancer]; Pfizer [Colon cancer]; Phanes [Colon cancer]; Promega [Tumor-agnostic and colon cancer]; Roche [Colon cancer]; Simcere [Tumor-agnostic cancer and colon cancer]; Takeda [Colon cancer]; Tempus [Tumor-agnostic cancer]. All of the relevant financial relationships listed have been mitigated. **Katrina S Pedersen, MD, MS** Consultant/Advisory Boards: GlaxoSmithKline [Colorectal cancer]; SAGA Diagnostics [Colorectal cancer]; Taiho [Colorectal cancer]. All of the relevant financial relationships listed have been mitigated. **Laurel Fisher, MD** Consultant/Advisory Boards: Medtronic [Provider use and software]. All of the relevant financial relationships listed have been mitigated. **Richard M Goldberg, MD** Equity Ownership/Stock Options: Advanced Chemotec Inc [Pancreatic cancer]; Compass Therapeutics [Biliary tract and colorectal cancer]. Consultant/Advisory Boards: AbbVie [GI cancers]; Advanced Chemotherapy Technologies [GI cancer]; AstraZeneca [GI cancer]; Bayer [GI cancer]; Compass Therapeutics [GI cancer]; Eisai [GI cancer]; G1 Therapeutics [GI cancer]; GSK [Colorectal cancer]; Innovative Cellular Therapeutics [Colorectal cancer]; Inspirna [Colorectal cancer]; Merck [GI cancer]; Modulation Therapeutics [Lymphoma]; Novartis [GI cancer]; Sorrento Therapeutics [GI cancer]; Taiho [GI cancer]. Other Financial Interest: Taiho [Expert testimony GI cancer]. All of the relevant financial relationships listed have been mitigated. **Tracy Jaffe, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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