Epidemiology, clinical features, and types of small bowel neoplasms

AUTHORS: Michael J Overman, MD, Hiroko Kunitake, MD
SECTION EDITOR: Kenneth K Tanabe, MD
DEPUTY EDITOR: Sonali M Shah, MD

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: **Apr 24, 2023.**

INTRODUCTION

The diagnosis of small bowel tumors is often difficult due to the rarity of these lesions and the nonspecific and variable nature of the presenting signs and symptoms. Thus, delay in diagnosis is common, which may result in the discovery of disease at a late stage and a poor treatment outcome.

Several tumors can arise within the small bowel, both malignant (adenocarcinomas, neuroendocrine tumors, lymphomas, and sarcomas) and benign (adenomas, leiomyomas, lipomas). Epidemiology, clinical manifestations, and specific tumor types will be reviewed here. Diagnosis, staging, and management of small bowel tumors are discussed separately. (See "Diagnosis and staging of small bowel neoplasms" and "Treatment of small bowel neoplasms".)

TYPES OF TUMORS

A variety of tumors, both malignant and benign, may arise within the small intestine.

Malignant tumors — The distribution of histologic types of small bowel malignant tumors is changing, largely because of the increasing incidence of neuroendocrine (carcinoid) tumors (NETs). In 1987, the most common histologic types of malignant tumors of the small intestine in population-based registry data from the Surveillance, Epidemiology and End Results (SEER)

program of the National Cancer Institute (NCI) were adenocarcinoma 45 percent, NET 29 percent, lymphoma 16 percent, and sarcoma 10 percent [1].

In the year 2000, NETs surpassed adenocarcinomas as the most common small bowel tumor reported to the National Cancer Database (NCDB) [2]. Between 1985 and 2005, the proportion of patients with NETs increased from 28 to 44 percent, while the proportion of adenocarcinoma decreased from 42 to 33 percent. The proportion of patients with stromal tumors and lymphoma remained essentially stable (17 and 8 percent, respectively).

Although these malignancies may be found throughout the different regions of the intestine, certain subtypes have a predilection for specific regions [1,3]. Adenocarcinoma is the most common malignancy affecting the duodenum, and NET is the most common tumor in the ileum, while sarcomas and lymphomas can develop throughout the entire small bowel [2,4]. The distribution of tumor subtypes according to small bowel location in a combined analysis of data from three registry-based series (the NCDB [1985 to 2005] and United States SEER [1973 to 2005] cohorts, and the Connecticut Tumor Registry [1980 to 2000] [5-7]) is depicted in the figure (figure 1) [8].

Largely as a result of these differences in distribution, the reported relative incidence of each histology varies considerably with the patient population under study [5,9,10].

Benign lesions — Benign lesions that may arise in the small bowel include adenomas, hamartomas, leiomyomas, fibromas, and lipomas [11].

EPIDEMIOLOGY

The following sections will discuss general aspects of the epidemiology of small bowel tumors. Specific epidemiologic aspects of the individual tumor types are discussed below.

Malignancies involving the small intestine are rare. In the United States, there are approximately 12,000 new cases and 2000 deaths from small bowel cancer annually [12]. Although the small intestine represents approximately 75 percent of the length and over 90 percent of the surface area of the alimentary tract, small bowel malignancies account for approximately 3 percent of all gastrointestinal tract neoplasms [12,13].

By contrast, over 150,000 new cases of large bowel cancer are diagnosed each year in the United States [12]. Several theories, based upon the unique microenvironment of the small intestine, have been proposed to explain the low rate of small bowel neoplasms relative to large bowel cancer [1,14]:

- The more dilute and liquid contents of the small bowel may cause less mucosal irritation than the more solid contents of the colon.
- The relatively rapid transit of intestinal contents through the small bowel may provide for a shorter exposure to carcinogens.
- The much lower bacterial load (particularly anaerobic bacteria) in the small bowel may result in less conversion of bile acids into potential carcinogens by anaerobic organisms.
- Benzpyrene, a known carcinogen present in food, is converted to less toxic metabolites by benzpyrene hydroxylase, which is present in higher concentrations in the small intestine compared with the stomach and colon.
- The increased lymphoid tissue and secretory immunoglobulin A (IgA), found in large quantities in the small bowel, may be protective.

While rates of large bowel cancer have been stable or decreasing over time, the incidence of small bowel cancer appears to be increasing, at least in the United States [2,5,6,15-17]. In older studies, reported age-adjusted incidence rates of small bowel cancer ranged from 1 to 3 per 100,000 population [4,9,16]. However, in a study analyzing the Connecticut Tumor Registry, a marked rise in the incidence of small bowel tumors over time was noted, with an incidence in the most recent time interval (1994 to 2000) of 14.8 cases per 100,000 population [5].

The degree to which the increased incidence is related to advances in diagnostic imaging is not known. However, much of the increase appears to be driven by a rising incidence of small bowel neuroendocrine tumors (NETs) [2]. (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts", section on 'Epidemiology' and 'Malignant tumors' above.)

The mean age at diagnosis of a small bowel neoplasm is 65 years old, with sarcoma and lymphoma presenting at a slightly younger age (60 to 62) than adenocarcinoma and NETs (67 to 68) [5,10]. There is a slight male predominance (male to female ratio of 1.5:1 [16]), and a number of studies report a higher incidence in Black than in White patients [1,16].

As a general rule, patients with small bowel adenocarcinoma have a higher incidence of secondary malignancies involving the colon, rectum, ampulla of Vater, endometrium, and ovary [18,19]. Conversely, patients with colon adenocarcinoma have an increased risk of small bowel adenocarcinoma [20]. These findings suggest that similar underlying genetic or environmental factors are involved in the carcinogenesis of adenocarcinomas arising in both the small and large intestine. A number of known heritable cancer syndromes are associated with

adenocarcinoma of both the large and small bowel, including hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and Peutz-Jeghers syndrome. (See 'Pathogenesis, risk factors, and predisposing conditions' below.)

PATHOGENESIS, RISK FACTORS, AND PREDISPOSING CONDITIONS

The etiology of most small bowel tumors is unknown, although a number of risk factors and predisposing conditions have been described.

Adenocarcinoma

The adenoma-carcinoma sequence — Most small bowel adenocarcinomas arise from adenomas, and the available data suggest an adenoma-carcinoma sequence driven by a multistep process of specific genetic changes similar to that described for colorectal cancers, but less well documented or understood (figure 2) [8,21]. Single, specific germline mutations underlie some common inherited syndromes (eg, familial adenomatous polyposis [FAP], hereditary nonpolyposis colorectal cancer [HNPCC]), while sporadic cancers result from the stepwise accumulation of multiple somatic mutations, possibly acquired as a result of exposure to carcinogens within the intestinal lumen. (See "Molecular genetics of colorectal cancer".)

As is seen in colon cancer, the increasing size of adenomas and the presence of villous features are both risk factors for the development of invasive carcinoma within an adenoma [22]. (See "Overview of colon polyps".)

Molecular profiling — Increasingly, biomarker expression is driving therapeutic decision making in patients with advanced refractory cancer. Small bowel adenocarcinomas have a different genomic profile compared with colorectal and gastric adenocarcinomas, including variations in the frequency and types of alterations of *KRAS*, adenomatosis polyposis coli (*APC*), *BRAF*, human epidermal growth factor receptor 2 (*ERBB2*/*HER2*), *ERBB3*, and other genes [23,24]. These variations might be contributing to the disparities in outcomes among these tumor types, and they also might provide some opportunity for targeted therapeutics in this disease. (See "Treatment of small bowel neoplasms", section on 'Molecular profiling and targeted therapies'.)

In one report, a total of 7559 patients (317 small bowel adenocarcinomas, 889 gastric carcinomas, and 6353 colorectal cancers) were analyzed on either a 236 or 315 cancer-related gene panel by Foundation Medicine, and alterations were compared across these three tumor types.

- The main differences in the frequency of genomic alterations between small bowel adenocarcinoma and colorectal cancer were in the *APC* (26.8 percent in small bowel versus 75.9 percent in colorectal cancer, p<0.001) and cyclin-dependent kinase inhibitor 2A (*CDKN2A*; 14.5 percent in small bowel versus 2.6 percent in colorectal cancer, p<0.001) genes.

- The main differences between small bowel adenocarcinoma and gastric cancer were in *KRAS* (53.6 percent in small bowel versus 14.2 percent in gastric cancer, p<0.001), *APC* (26.8 versus 7.8 percent, p<0.001), and mothers against decapentaplegic homolog 4 (*SMAD4*; 17.4 versus 5.2 percent, p<0.001).

- Molecular differences between small bowel subsites (duodenum, jejunum, ileum) were minimal, suggesting common genomic features across the small bowel.

In a separate report, exome sequencing performed on 106 primary small bowel adenocarcinomas demonstrated four mutational signatures: signature 6, associated with mismatch repair (MMR) deficiency; signature 1A, associated with older age; and signatures 17 and U2, two signatures of unknown cause [24].

These efforts demonstrate small bowel adenocarcinomas to have their own molecular profile differing from other neighboring gastrointestinal tract cancers.

Hereditary cancer syndromes — An increased risk of adenocarcinoma is seen in a number of familial cancer syndromes, many of which are linked to specific inherited genetic abnormalities:

- HNPCC is an inherited condition characterized by loss of DNA MMR, which is caused by a germline mutation in one allele of a MMR gene and inactivation of the second allele by mutation, loss of heterozygosity, or epigenetic silencing by promoter hypermethylation. The biologic footprint of deficient DNA MMR is high levels of microsatellite instability (MSI-H). Affected individuals are at risk for colorectal cancer and for several extracolonic cancers, including adenocarcinomas of the small bowel and endometrium. As with colorectal cancer, HNPCC is thought to be responsible for approximately 5 to 10 percent of small bowel adenocarcinomas [25,26]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis".)

- The Peutz-Jeghers syndrome is an autosomal dominant polyposis disorder characterized by multiple hamartomatous polyps throughout the intestinal tract and a marked increase risk for adenocarcinoma of both the large and small bowel [27]. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

- FAP is associated with a germline mutation in the *APC* gene that promotes tumor formation in primarily the large intestine but also the duodenum. These patients have multiple duodenal polyps (with a predilection for the ampullary region), which can undergo malignant transformation into an adenocarcinoma. In addition, patients with FAP are predisposed to the development of desmoid tumors, which develop within the small bowel or its mesentery and are often multiple in number (image 1) [28,29]. (See "Desmoid tumors: Epidemiology, molecular pathogenesis, clinical presentation, diagnosis, and local therapy" and "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Ampullary adenomas: Clinical manifestations and diagnosis".)

Dietary factors, tobacco, and obesity — A number of dietary factors have been associated with an increased risk of a small bowel cancer in case-control studies, including intake of alcohol, refined sugar, red meat, and salt-cured and smoked foods [14,17,30,31]. Tobacco use was associated with cancer risk in two studies, while others suggest no increased risk in smokers [30,32,33]. Studies on the relationship between obesity and small bowel malignancy are conflicting, with some showing an increased risk in obese patients [34-36], some a decreased risk [33], and others no effect [14].

Cystic fibrosis — Patients with cystic fibrosis have an elevated risk of small bowel cancer. In a meta-analysis, the pooled standardized incidence ratio was 18.94, 95% CI 9.37-38.27, and it was two- to fivefold higher following lung transplantation [37]. (See "Cystic fibrosis: Overview of gastrointestinal disease", section on 'Gastrointestinal cancer'.)

Chronic inflammation — A role for chronic inflammation in the etiology of both adenocarcinoma and lymphoma is suggested by the fact that small bowel disorders characterized by chronic mucosal inflammation predispose to malignancy. Inflammatory bowel disease, in particular Crohn disease, predisposes to adenocarcinoma within the involved area of the small intestine. The risk increases with both the extent and duration of small bowel involvement [38-40]. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults".)

An increased risk of small bowel lymphoma is seen in patients with chronic immunodeficiency states and autoimmune disorders, including celiac disease [41,42]. Patients with celiac disease also have a higher risk for small bowel adenocarcinoma [43]. (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas" and "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

Neuroendocrine tumors — The pathogenesis and risk factors for neuroendocrine tumors arising in the small bowel are almost entirely unknown, apart from an association with multiple

endocrine neoplasia type I (MEN-I) in rare cases [44,45]. (See "Multiple endocrine neoplasia type 1: Clinical manifestations and diagnosis".)

CLINICAL PRESENTATION

The general aspects of the clinical presentation of benign and malignant small bowel tumors are discussed here. Specific symptoms associated with individual tumor types are discussed below. (See 'Types of tumors' above.)

The most common presenting symptom of a small bowel tumor is abdominal pain, which is present in 44 to 90 percent of patients [46-49]. Pain is typically intermittent and crampy in nature. Weight loss occurs in 24 to 44 percent, nausea and vomiting in 17 to 64 percent, and gastrointestinal bleeding in 23 to 41 percent. Intestinal obstruction is more common than perforation, occurring in 22 to 26 percent compared with 6 to 9 percent, respectively [46-48].

As compared with those with benign tumors, patients with malignant small bowel neoplasms are more often symptomatic, and the majority of symptomatic small bowel tumors are malignant [46,50]. Furthermore, symptoms at presentation tend to differ between benign and malignant tumors. As an example, in a report of 49 patients with a small bowel neoplasm (17 benign and 32 malignant), 47 percent of benign tumors were asymptomatic (versus 6 percent of malignant tumors), and when symptomatic, they more commonly presented with acute gastrointestinal hemorrhage (29 versus 6 percent of malignant tumors). Malignant tumors more commonly presented with abdominal pain (63 versus 24 percent) and weight loss (38 versus 0 percent). Despite these data, clinical presentation alone does not permit the distinction between a benign versus a malignant lesion.

The often vague and nonspecific nature of the symptoms makes early diagnosis of a malignant small bowel tumor difficult. There may be a significant delay from onset of symptoms to diagnosis (in one series, averaging 30 weeks [46]). As a result, by the time a patient becomes symptomatic, their disease is usually advanced, with either involvement of regional lymph nodes or distant metastatic sites.

The differential diagnosis is broad given the nonspecific symptoms. More common causes of small bowel stricturing or obstruction include adhesions, hernia entrapment, inflammatory bowel disease, endometriosis, splenosis, and complications from appendicitis or diverticulitis.

ADENOCARCINOMA

Adenocarcinomas represent from 25 to 40 percent of primary small bowel malignancies [1,2,5,9,10,49,51]. They usually present between the ages of 50 to 70, and there is a slight male predominance. Age of onset tends to be lower in patients with predisposing conditions, such as Crohn disease [25,27,52,53].

As noted above, the risk of small bowel adenocarcinoma is higher in patients who have had colorectal cancer, suggesting a possible common etiology [20]. (See 'Epidemiology' above.)

Also as noted above, inherited syndromes, such as hereditary nonpolyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP), are responsible for fewer than 10 percent of small bowel adenocarcinomas [54,55]. Patients with HNPCC are at increased risk for adenocarcinoma throughout the small bowel, while FAP increases the risk for both adenomas and adenocarcinomas of the duodenum. (See 'Hereditary cancer syndromes' above.)

Location — The incidence of adenocarcinoma is highest in the duodenum (picture 1) and decreases progressively throughout the rest of the small intestine. In two large single-institution series of patients with small bowel adenocarcinoma, 65 and 57 percent of cases arose in the duodenum [56,57].

Explanations for the predilection to the initial part of the small bowel include the metabolism or dilution of ingested carcinogens in transit through the small bowel or interactions of carcinogens with pancreaticobiliary secretions [58]. The possible etiologic role of pancreaticobiliary secretions is supported by a study evaluating 213 cases of duodenal adenocarcinoma identified from the Los Angeles County Tumor Registry, in which the exact subsite within the duodenum was identified. Fifty-seven percent of cases occurred in the second portion of the duodenum, consistent with a primarily periampullary distribution [58].

Crohn disease — An exception to the predominantly proximal location is in patients with Crohn disease. Seventy percent of adenocarcinomas that arise in this setting are in the ileum, the primary site of the inflammatory process. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)

The development of an adenocarcinoma in patients with Crohn disease should be suspected in those with longstanding disease who develop a change in their clinical status, such as an obstruction that fails to resolve with usual medical treatments [59,60]. The risk for adenocarcinoma is directly related to both the extent of small bowel involvement and the duration of Crohn disease. In one report, the cumulative risk of a small bowel adenocarcinoma in patients with small bowel Crohn disease was 0.2 percent at 10 years and 2.2 percent at 25 years [61]. The diagnosis is rarely made preoperatively since the symptoms are similar to those

of Crohn disease with an inflammatory or fibrous stricture [52]. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults".)

Presenting symptoms — The clinical presentation of adenocarcinoma of the small bowel is nonspecific, with the most frequent symptom being abdominal pain. In a series of 491 patients with small bowel adenocarcinoma, presenting symptoms were as follows [57]:

- Abdominal pain – 43 percent
- Nausea and vomiting – 16 percent
- Anemia – 15 percent
- Overt gastrointestinal tract bleeding – 7 percent
- Jaundice – 6 percent
- Weight loss – 3 percent
- Other or no symptoms – 9 percent

An obstructed duodenal adenocarcinoma may present with vomiting due to a gastric outlet obstruction, while in those with more distal lesions, severe cramping abdominal pain may be the presenting symptom. Intestinal obstruction can be caused by progression of an apple core lesion (image 2) or by a large intraluminal polypoid mass.

Largely because of the vague nature of symptoms, the majority of patients have advanced disease (stage III or IV (table 1)) at diagnosis. In a large series of patients with small bowel adenocarcinoma derived from the National Cancer Database (NCDB), the distribution of stage at diagnosis was as follows [62]:

- Stage 0 – 3 percent
- Stage I – 12 percent
- Stage II – 27 percent
- Stage III – 26 percent
- Stage IV – 32 percent

The diagnostic and staging evaluation and treatment of small bowel adenocarcinoma is discussed elsewhere. (See "Diagnosis and staging of small bowel neoplasms".)

NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) of the small bowel have a morphologically unique appearance and are characterized by the production of biologically active amines, which are stored in

neurosecretory granules. Secretion of these products by the tumor cells can result in a variety of clinical syndromes caused by the secreted product:

- The vast majority are well-differentiated (grade 1 or 2) gastrointestinal NETs (GINETs), previously termed carcinoid tumors (table 2). Carcinoid syndrome is the term applied to a constellation of symptoms mediated by various humoral factors elaborated by some well-differentiated NETs of the digestive tract and lungs, which synthesize, store, and release a variety of polypeptides, biogenic amines, and prostaglandins (table 3). Some of these tumor products are responsible for carcinoid syndrome, but the relative contributions of each and the specificity of any for particular components of the syndrome are uncertain (table 4). More than 90 percent of patients with carcinoid syndrome have metastatic disease from a small bowel primary NET, typically to the liver. (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on '2010 and 2019 World Health Organization classification' and "Clinical features of carcinoid syndrome" and "Diagnosis of carcinoid syndrome and tumor localization".)

- Other functioning NETs of the small bowel that produce specific clinical syndromes are rare when compared with these well-differentiated GINETs. The most common is a gastrinoma of the duodenum, which is defined by the associated clinical syndrome of excess gastrin secretion (Zollinger-Ellison syndrome). Although the majority of gastrinomas, 85 percent, are localized to the pancreas, approximately 15 percent will be found in the upper duodenum. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis".)

- Other even more rarely reported NETs arising in the small bowel include duodenal somatostatinomas, paragangliomas, and high-grade (poorly differentiated) neuroendocrine carcinomas, which are rarely, if ever, functioning (table 2). (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on '2010 and 2019 World Health Organization classification' and "Somatostatinoma: Clinical manifestations, diagnosis, and management" and "High-grade gastroenteropancreatic neuroendocrine neoplasms".)

Well-differentiated gastrointestinal neuroendocrine tumors — Most GINETs arising in the small bowel are typically well-differentiated (grade 1 or 2 (table 5)) NETs, most of which are characterized by an indolent disease course [63]. Notably, duodenal NETs may have a more heterogenous disease course, with a high rate of metastasis both at the time of diagnosis and following resection, even if well differentiated [64].

In modern series, NETs represent approximately 40 percent of primary small intestinal malignancies [2,5,9,10]. They have been reported in patients from 20 to 80 years old, with the highest incidence in the 60s.

Grossly, these tumors appear as firm intramucosal or submucosal nodules, with a yellow cut surface due to their high lipid content. They tend to infiltrate the bowel wall and may extend through the serosa, causing shortening and thickening of the mesentery due to an intense associated desmoplastic reaction (image 3). Microscopically, solid nests of uniform small cells with round or oval nuclei are present with a surrounding intense desmoplastic reaction (picture 2). They demonstrate little or no cellular pleomorphism, hyperchromasia, or increased mitotic activity. (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system".)

Small bowel well-differentiated GINETs are most commonly found in the ileum, within 60 cm of the ileocecal valve. The presence of multiple synchronous nodules in 30 percent of patients mandates careful inspection of the entire small intestine to exclude other sites of disease [54].

Because of their indolent growth, most well-differentiated small bowel GINETs are asymptomatic at presentation (ie, there are no symptoms of local obstruction or carcinoid syndrome) and found only incidentally. Symptoms generally relate to mass effects from the primary or metastatic tumors, or they may be caused by tumor production of bioactive amines (carcinoid syndrome):

- The most common syndrome caused by tumor production of bioactive amines is carcinoid syndrome, which usually does not occur until the bioactive amines have gained access to the systemic circulation (typically in the setting of liver metastases). The most common symptoms are watery diarrhea and flushing. (See "Clinical features of carcinoid syndrome".)

- In symptomatic patients who do not have carcinoid syndrome, abdominal pain is the most common initial symptom, occurring in approximately 40 percent [55]. The pain is most often vague and nonspecific. Intermittent obstruction occurs in 25 percent of all small intestinal well-differentiated GINETs. Obstruction may be caused by intraluminal tumor, but often results from mesenteric kinking and distortion brought on by tumor invasion and a secondary desmoplastic response [65]. The latter produces a characteristic radiographic abnormality: a combination of abrupt angulation with a filling defect in the small bowel (image 4).

- Pain may also arise from vascular compromise secondary to large bulky mesenteric nodal metastasis, mesenteric vascular invasion, and/or microvascular metastasis. Possibly

contributing to the ischemic process is the vasospastic effect of serotonin produced by the tumor (see below).

Metastatic disease, which is present in 90 percent of symptomatic patients with carcinoid syndrome, correlates not only with the depth of invasion and location, but also the size of the primary lesion. For NETs <1 cm, the risk of distant metastasis is 0 to 2 percent for appendiceal as compared with 15 to 18 percent for small bowel primaries. In contrast, once NETs exceed 2 cm, 47 percent of small bowel primaries will have metastasized to liver; lungs and bone are affected less frequently (table 6).

The current (2017) Tumor, Node, Metastasis (TNM) classification and staging of small bowel NETs (as adopted by the American Joint Committee on Cancer [AJCC], the Union for International Cancer Control [UICC] [66], and the European Neuroendocrine Tumor Society [ENETS] [67]) includes separate staging tables for NETs of the duodenum/ampulla (table 7) [68] and tumors arising in the jejunum and ileum (table 8) [69].

The clinical characteristics of well-differentiated small bowel GINETs are addressed in more detail separately. (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts", section on 'Jejunoileal small bowel tumors'.)

Carcinoid syndrome — Well-differentiated GINETs are characterized by their ability to secrete serotonin and other bioactive products (table 3); the majority of patients with carcinoid syndrome have metastatic disease, typically involving the liver. This is because symptoms are most common when the secretory products of these tumors gain direct access to the systemic circulation, thus avoiding metabolism in the liver. This scenario occurs most commonly in the presence of hepatic metastases. (See "Clinical features of carcinoid syndrome", section on 'Pathophysiology'.)

However, at least some data support the view that carcinoid syndrome might be more common in locoregional disease than previously thought. This was illustrated in a population-based series of 9512 GINETs arising in individuals aged 65 or over and derived from the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database [70]. Among patients with small bowel primary NETs, the rates of carcinoid syndrome at diagnosis for patients with localized, regional, and distant disease were 155 of 817 (19 percent), 248 of 670 (37 percent), and 242 of 436 (56 percent), respectively. These data suggest that unappreciated hepatic metastases or carcinoid syndrome in locoregional disease may be more common than previously reported [71-73], especially in small bowel primaries.

The most common symptoms associated with carcinoid syndrome are watery diarrhea and flushing (table 4). The flush is often dramatic and manifests as an intense purplish color on the upper body and arms; it can be precipitated by consuming alcohol, blue cheese, chocolate, or red wine or with exercise. Repeated attacks can lead to the development of telangiectasias and permanent skin discoloration. (See "Clinical features of carcinoid syndrome".)

A life-threatening form of carcinoid syndrome called carcinoid crisis is usually precipitated by a specific event, such as anesthesia, surgery, or chemotherapy. The manifestations include an intense flush, diarrhea, tachycardia, hypertension or hypotension, bronchospasm, and alteration of mental status. Prevention and management are discussed elsewhere. (See "Treatment of the carcinoid syndrome", section on 'Carcinoid crisis: prevention and management'.)

PRIMARY GASTROINTESTINAL TRACT LYMPHOMA

Lymphoma may arise as a primary neoplasm in the intestinal tract or as a component of systemic disease with gastrointestinal (GI) involvement. The diagnosis of a primary GI lymphoma requires the following [74]:

- No peripheral or mediastinal lymphadenopathy
- A normal white blood cell count and differential on the peripheral blood smear
- Tumor involvement must be predominantly in the GI tract
- No evidence of liver or spleen involvement [75,76]

Primary GI tract lymphoma is the most common extranodal form of lymphoma; the stomach and small bowel are the most common sites. As an example, in a study of 371 patients registered in a German multicenter treatment study for GI lymphomas, the following sites were involved [77] (see "Clinical presentation and diagnosis of primary gastrointestinal lymphomas"):

- Stomach – 75 percent
- Small bowel (including duodenum) – 9 percent
- Ileocecal region – 7 percent
- More than one GI site – 6 percent
- Rectum – 2 percent
- Diffuse colonic involvement – 1 percent

In the Middle East, 75 percent of GI lymphomas originate in the small bowel and are associated with immunoproliferative small intestinal disease (IPSID); synonyms include Mediterranean lymphoma and alpha heavy chain disease. By contrast, small intestinal lymphomas are less

common in industrialized nations and are not of the IPSID type. (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas".)

In the United States, small bowel lymphoma occurs predominantly in adults, peaking in the seventh decade, and 60 percent of patients are male [78]. Some of the predisposing conditions include:

- Autoimmune diseases
- Immunodeficiency syndromes (eg, acquired immunodeficiency syndrome [AIDS])
- Long-standing immunosuppressive therapy (eg, post-transplantation)
- Crohn disease
- Radiation therapy
- Nodular lymphoid hyperplasia

The incidence of primary intestinal lymphoma in the United States doubled between 1985 and 1990 [79]. Among the factors implicated in this increase are the increasing number of immunocompromised patients (eg, AIDS, transplantation recipients) and the increasing immigration from resource-limited countries.

Lymphomas arise from the lymphoid aggregates in the submucosa. The distribution of lymphoma in the small intestine parallels the distribution of lymphoid follicles, with the lymphoid-rich ileum representing the most common location. As with sarcoma, lymphomas are characteristically bulky tumors; approximately 70 percent are larger than 5 cm in diameter at presentation.

Most patients present with abdominal pain, anorexia, and weight loss (table 9). Less commonly, infiltration of the mucosa can result in ulceration and bleeding, and extension to the serosa and adjacent tissues may result in a large obstructing mass with or without intussusception and crampy abdominal pain (image 5A-B). The risk of perforation depends on the site of GI tract involvement; perforation is seen in 9 percent of small bowel lymphomas and only 2 percent of gastric lymphomas [77]. (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas".)

Histologically, these non-Hodgkin lymphomas may be low or high grade, and they may be of B-cell or T-cell origin. The Revised European-American Lymphoma (REAL)/World Health Organization (WHO) classification system, as is used for other non-Hodgkin lymphomas, is predominantly used for classification [80,81], although an alternative classification system for primary GI lymphomas has been proposed [82]. The B-cell lymphomas that most often involve the GI tract consist of the mucosa associated lymphoid tissue (MALT) type, diffuse large B-cell, mantle cell, and Burkitt and Burkitt-like variants. MALT type tumors occur most often in the

stomach, while mantle cell lymphoma has a predilection for the colon and small intestine. The less common T-cell lymphomas are most often jejunal. Primary or secondary involvement of the GI tract by Hodgkin lymphoma is extremely rare [83]. (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas".)

Histologic and clinical factors associated with prognosis include histological subtype of non-Hodgkin lymphoma, histologic grade of differentiation, stage of disease, and International Prognostic Index (IPI). (See "Treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)".)

SARCOMA

Malignant mesenchymal tumors (sarcomas) represent approximately 10 percent of small bowel neoplasms [1,5,10,49,62,84] and are most common in the jejunum, the ileum, and a Meckel's diverticulum [85]. The most common type of intestinal sarcoma is gastrointestinal stromal tumor (GIST), accounting for 83 to 86 percent of cases [2,86].

Prior to the identification of GISTs by their molecular characteristics, leiomyosarcomas represented the most common small bowel sarcoma. However, the majority of these previously classified leiomyosarcomas in older studies are actually GIST tumors. In a report of 1091 tumors originally classified as "smooth muscle tumors of the small intestine," 906 (83 percent) were GISTs [86]. Among the 176 non-GISTs, there were 53 sarcomas (mostly phenotypically undifferentiated), 32 leiomyosarcomas (3 percent of the total), 13 leiomyomas, 14 sarcomatoid epithelial neoplasms, 13 desmoids, 8 schwannomas, and a variety of other unusual benign and malignant proliferations. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors".)

Histologically, GISTs can have a similar morphologic appearance to leiomyosarcomas (picture 3) and, thus, must be differentiated based on the expression of c-kit (the CD117 antigen), which represents a component of the KIT tyrosine kinase receptor. Activating mutations in the *KIT* oncogene are seen in over 80 percent of all GISTs. A subset of GISTs lacking *KIT* mutations have activating mutations in a related receptor tyrosine kinase, the platelet derived growth factor receptor alpha (PDGFRA). (See "Diagnosis and staging of small bowel neoplasms", section on 'Histology and differential diagnosis'.)

Common presenting symptoms of small bowel sarcomas, including GISTs, include pain, weight loss, bleeding, perforation, or a palpable mass [87]. Because they tend to enlarge extraluminally, obstruction is rare and typically a late-presenting symptom.

METASTATIC LESIONS

Secondary neoplastic involvement of the small intestine is more common than is primary small intestinal neoplasia, given the rarity of small bowel neoplasms. Extraluminal involvement of the small bowel is particularly common in the setting of widespread peritoneal carcinomatosis. Erosion through the bowel wall into the lumen can occur, particularly with tumors that have a predilection to involve the peritoneal cavity, such as ovarian, colon, and gastric cancer.

Hematogenous spread to the bowel is also possible. In studies in which direct extension from peritoneal metastases was excluded, the most common tumors to hematogenously spread to the small bowel were melanoma, lung, breast, cervix, sarcoma, and colon [88-90]. The small bowel is the most common site of gastrointestinal metastases in patients with metastatic melanoma (image 6) [91,92]. (See "Metastatic melanoma: Surgical management", section on 'Gastrointestinal tract'.)

BENIGN TUMORS

The frequency of benign tumors of the small bowel increases from the duodenum to the ileum [93]. Of the various histologic types, adenomas, leiomyomas, and lipomas are the most common.

Adenomas — There are three major types of benign small bowel adenomas: simple villous, tubular, and Brunner's gland adenomas.

Villous adenomas carry a significant potential for malignant transformation. Malignant cells are found in as many as 42 percent of duodenal villous adenomas [94], with an adenoma-carcinoma sequence comparable to that of colorectal cancer [95]. Familial adenomatous polyposis (FAP) is a risk factor; 80 percent of affected patients develop duodenal adenomas, which are often multiple [96]. Adenomas in the duodenum have a predilection for the papilla (ampulla of Vater). (See "Ampullary adenomas: Clinical manifestations and diagnosis" and "Familial adenomatous polyposis: Screening and management of patients and families".)

Coincident colonic adenomas are common in patients who have villous adenomas of the papilla or duodenum, suggesting that colonoscopy is an important component of the diagnostic workup. The usual presentation is with bleeding or obstruction of either the small bowel or biliary tract. On biopsy, the superficial part of the lesion may appear benign, with areas of adenocarcinoma in the deeper parts [94].

Tubular adenomas have a lower malignant potential. They are most common in the duodenum, and are usually asymptomatic, but may present with bleeding or obstruction.

There are no firm guidelines regarding the management of sporadic duodenal adenomas, though many gastroenterologists will remove them endoscopically in the absence of endoscopic features suggesting possible malignancy. Additionally, there are no definitive guidelines regarding the size of endoscopically resectable adenomas; however, most authors recommend that lesions ≥4 cm should not be treated endoscopically [97].

Endoscopic retrograde cholangiopancreatography, endoscopic ultrasound, intraductal ultrasound, and chromoendoscopy can all provide useful information in the evaluation of ampullary adenomas, including the extent of intraductal progression of the adenoma. (See "Ampullary adenomas: Management" and "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging", section on 'Endoscopic ultrasonography'.)

Patients with sporadic duodenal adenomas should also be screened for colorectal cancer as they are at increased risk for colorectal neoplasia [98-100].

A Brunner's gland adenoma is a rare small bowel neoplasm. It is caused by hyperplasia of the exocrine glands within the proximal duodenal mucosa. (See "Ampullary adenomas: Clinical manifestations and diagnosis".)

Leiomyomas — Leiomyomas are single, firm, gray or white, well-defined masses that arise in the submucosal layer of the wall of the small intestine (image 7). Microscopically, they consist of well-differentiated smooth muscle cells (picture 4). These tumors usually enlarge extraluminally and, therefore, are not detected until they outgrow their blood supply, causing central necrosis, ulceration, and bleeding into the bowel lumen.

In cases in which the tumor extends intraluminally, obstruction may be the initial symptom (picture 5). (See "Etiologies, clinical manifestations, and diagnosis of mechanical small bowel obstruction in adults".)

Leiomyomas are rare; in the series described above, they accounted for only 13 of the 1091 tumors originally classified as smooth muscle tumors of the small intestine (approximately 1 percent) [86].

Lipomas — Lipomas are the second most common benign tumor arising in the small bowel, and they occur mostly in the ileum and duodenum. They arise from either submucosal adipose tissue or serosal fat and may present with obstruction, small bowel bleeding, or as an incidental finding. These are submucosal lesions with homogeneous fatty tissue on a cut surface. They

have a diagnostic low attenuation appearance on computed tomography (CT) scan (image 8A-B) [101].

Other benign lesions — Desmoid tumors, which are commonly seen in patients with FAP, may grow intraluminally, causing obstruction or, extraluminally, presenting as a palpable abdominal mass (image 1). (See "Desmoid tumors: Epidemiology, molecular pathogenesis, clinical presentation, diagnosis, and local therapy".)

Hemangiomas are rare lesions that usually present with bleeding. Hamartomas of the small intestine are seen in patients with the Peutz-Jeghers syndrome. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

SUMMARY

- A variety of tumors, both malignant and benign, may arise within the small intestine. The most common malignant tumors are well-differentiated neuroendocrine tumors (NETs), adenocarcinomas, lymphomas, and sarcomas. Benign lesions that may arise in the small bowel include adenomas, leiomyomas, fibromas, and lipomas. (See 'Types of tumors' above.)

- Malignancies involving the small intestine are rare; they account for only 2 percent of all gastrointestinal tract neoplasms and fewer than 0.4 percent of all cancers in the United States. (See 'Epidemiology' above.)

- The etiology of most small bowel cancers is unknown, although a number of risk factors and predisposing conditions have been described, particularly for small bowel adenocarcinomas. (See 'Hereditary cancer syndromes' above.)

- The most common presenting symptom of a small bowel tumor is abdominal pain, which is typically intermittent and crampy in nature. Other symptoms include weight loss, nausea and vomiting, gastrointestinal bleeding, and intestinal obstruction. As compared with those with benign tumors, patients with malignant small bowel neoplasms are more often symptomatic, and the majority of symptomatic small bowel tumors are malignant. (See 'Clinical presentation' above.)

- The incidence of adenocarcinoma is highest in the duodenum. The most common clinical presentation is abdominal pain; a duodenal adenocarcinoma may present as a gastric outlet obstruction. (See 'Adenocarcinoma' above.)

- Well-differentiated gastrointestinal NETs arising in the small bowel are most commonly found in the ileum, within 60 cm of the ileocecal valve. Because of their indolent growth, most are asymptomatic at presentation and found incidentally. When present, symptoms generally relate to mass effects, including intermittent obstruction. Tumor production of bioactive amines results in carcinoid syndrome (watery diarrhea, flushing, sweating, wheezing, dyspnea, abdominal pain, hypotension) only when the secretory products gain direct access to the systemic circulation, thus avoiding metabolism in the liver; this occurs most commonly in patients with extensive hepatic metastases. (See 'Well-differentiated gastrointestinal neuroendocrine tumors' above.)

- Lymphoma may arise as a primary neoplasm in the intestinal tract or as a component of systemic disease with gastrointestinal involvement. Primary gastrointestinal tract lymphoma is the most common extranodal form of lymphoma; the lymphoid-rich ileum is the most common location. (See 'Primary gastrointestinal tract lymphoma' above.)

- Malignant mesenchymal tumors (sarcomas) represent approximately 10 percent of small bowel neoplasms and are most common in the jejunum and ileum. The most common type of intestinal sarcoma is gastrointestinal stromal tumor. (See 'Sarcoma' above.)

- The frequency of benign tumors of the small bowel increases from the duodenum to the ileum. Villous adenomas carry a significant potential for malignant transformation. Patients with sporadic duodenal adenomas should be screened for colorectal cancer as they are at increased risk. (See 'Adenomas' above.)

ACKNOWLEDGMENT

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

REFERENCES

1. Weiss NS, Yang CP. Incidence of histologic types of cancer of the small intestine. J Natl Cancer Inst 1987; 78:653.
2. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 2009; 249:63.

3. McLaughlin PD, Maher MM. Primary malignant diseases of the small intestine. AJR Am J Roentgenol 2013; 201:W9.
4. Gabos S, Berkel J, Band P, et al. Small bowel cancer in western Canada. Int J Epidemiol 1993; 22:198.
5. Hatzaras I, Palesty JA, Abir F, et al. Small-bowel tumors: epidemiologic and clinical characteristics of 1260 cases from the connecticut tumor registry. Arch Surg 2007; 142:229.
6. Chow JS, Chen CC, Ahsan H, Neugut AI. A population-based study of the incidence of malignant small bowel tumours: SEER, 1973-1990. Int J Epidemiol 1996; 25:722.
7. Subramanian KN, Ghosh PK, Dhar R, et al. The primary structure of regions of SV 40 DNA encoding the ends of mRNA. Prog Nucleic Acid Res Mol Biol 1976; 19:157.
8. Raghav K, Overman MJ. Small bowel adenocarcinomas--existing evidence and evolving paradigms. Nat Rev Clin Oncol 2013; 10:534.
9. DiSario JA, Burt RW, Vargas H, McWhorter WP. Small bowel cancer: epidemiological and clinical characteristics from a population-based registry. Am J Gastroenterol 1994; 89:699.
10. Lepage C, Bouvier AM, Manfredi S, et al. Incidence and management of primary malignant small bowel cancers: a well-defined French population study. Am J Gastroenterol 2006; 101:2826.
11. Chung CS, Tai CM, Huang TY, et al. Small bowel tumors: A digestive endoscopy society of Taiwan (DEST) multicenter enteroscopy-based epidemiologic study. J Formos Med Assoc 2018; 117:705.
12. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73:17.
13. DeSesso JM, Jacobson CF. Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. Food Chem Toxicol 2001; 39:209.
14. Chow WH, Linet MS, McLaughlin JK, et al. Risk factors for small intestine cancer. Cancer Causes Control 1993; 4:163.
15. Severson RK, Schenk M, Gurney JG, et al. Increasing incidence of adenocarcinomas and carcinoid tumors of the small intestine in adults. Cancer Epidemiol Biomarkers Prev 1996; 5:81.
16. Haselkorn T, Whittemore AS, Lilienfeld DE. Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. Cancer Causes Control 2005; 16:781.
17. Neugut AI, Jacobson JS, Suh S, et al. The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev 1998; 7:243.

18. Scélo G, Boffetta P, Hemminki K, et al. Associations between small intestine cancer and other primary cancers: an international population-based study. Int J Cancer 2006; 118:189.
19. Zar N, Garmo H, Holmberg L, Hellman P. Risk of second primary malignancies and causes of death in patients with adenocarcinoma and carcinoid of the small intestine. Eur J Cancer 2008; 44:718.
20. Neugut AI, Santos J. The association between cancers of the small and large bowel. Cancer Epidemiol Biomarkers Prev 1993; 2:551.
21. Wheeler JM, Warren BF, Mortensen NJ, et al. An insight into the genetic pathway of adenocarcinoma of the small intestine. Gut 2002; 50:218.
22. Perzin KH, Bridge MF. Adenomas of the small intestine: a clinicopathologic review of 51 cases and a study of their relationship to carcinoma. Cancer 1981; 48:799.
23. Schrock AB, Devoe CE, McWilliams R, et al. Genomic Profiling of Small-Bowel Adenocarcinoma. JAMA Oncol 2017; 3:1546.
24. Hänninen UA, Katainen R, Tanskanen T, et al. Exome-wide somatic mutation characterization of small bowel adenocarcinoma. PLoS Genet 2018; 14:e1007200.
25. Rodriguez-Bigas MA, Vasen HF, Lynch HT, et al. Characteristics of small bowel carcinoma in hereditary nonpolyposis colorectal carcinoma. International Collaborative Group on HNPCC. Cancer 1998; 83:240.
26. Zhang MQ, Chen ZM, Wang HL. Immunohistochemical investigation of tumorigenic pathways in small intestinal adenocarcinoma: a comparison with colorectal adenocarcinoma. Mod Pathol 2006; 19:573.
27. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000; 119:1447.
28. Abrahams NA, Halverson A, Fazio VW, et al. Adenocarcinoma of the small bowel: a study of 37 cases with emphasis on histologic prognostic factors. Dis Colon Rectum 2002; 45:1496.
29. Kawashima A, Goldman SM, Fishman EK, et al. CT of intraabdominal desmoid tumors: is the tumor different in patients with Gardner's disease? AJR Am J Roentgenol 1994; 162:339.
30. Wu AH, Yu MC, Mack TM. Smoking, alcohol use, dietary factors and risk of small intestinal adenocarcinoma. Int J Cancer 1997; 70:512.
31. Cross AJ, Leitzmann MF, Subar AF, et al. A prospective study of meat and fat intake in relation to small intestinal cancer. Cancer Res 2008; 68:9274.
32. Chen CC, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomarkers Prev 1994; 3:205.

33. Negri E, Bosetti C, La Vecchia C, et al. Risk factors for adenocarcinoma of the small intestine. Int J Cancer 1999; 82:171.
34. Bjørge T, Tretli S, Engeland A. Height and body mass index in relation to cancer of the small intestine in two million Norwegian men and women. Br J Cancer 2005; 93:807.
35. Wolk A, Gridley G, Svensson M, et al. A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control 2001; 12:13.
36. Samanic C, Gridley G, Chow WH, et al. Obesity and cancer risk among white and black United States veterans. Cancer Causes Control 2004; 15:35.
37. Yamada A, Komaki Y, Komaki F, et al. Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis. Lancet Oncol 2018; 19:758.
38. Canavan C, Abrams KR, Mayberry JF. Meta-analysis: mortality in Crohn's disease. Aliment Pharmacol Ther 2007; 25:861.
39. Solem CA, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Small intestinal adenocarcinoma in Crohn's disease: a case-control study. Inflamm Bowel Dis 2004; 10:32.
40. Jess T, Winther KV, Munkholm P, et al. Intestinal and extra-intestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. Aliment Pharmacol Ther 2004; 19:287.
41. Green PH, Jabri B. Celiac disease and other precursors to small-bowel malignancy. Gastroenterol Clin North Am 2002; 31:625.
42. Howdle PD, Jalal PK, Holmes GK, Houlston RS. Primary small-bowel malignancy in the UK and its association with coeliac disease. QJM 2003; 96:345.
43. Green PH, Cellier C. Celiac disease. N Engl J Med 2007; 357:1731.
44. Heymann MF, Hamy A, Triau S, et al. Endocrine tumors of the duodenum. A study of 55 cases relative to clinicopathological features and hormone content. Hepatogastroenterology 2004; 51:1367.
45. Leoncini E, Carioli G, La Vecchia C, et al. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. Ann Oncol 2016; 27:68.
46. Ciresi DL, Scholten DJ. The continuing clinical dilemma of primary tumors of the small intestine. Am Surg 1995; 61:698.
47. Minardi AJ Jr, Zibari GB, Aultman DF, et al. Small-bowel tumors. J Am Coll Surg 1998; 186:664.
48. Ojha A, Zacherl J, Scheuba C, et al. Primary small bowel malignancies: single-center results of three decades. J Clin Gastroenterol 2000; 30:289.

49. Talamonti MS, Goetz LH, Rao S, Joehl RJ. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. Arch Surg 2002; 137:564.

50. DARLING RC, WELCH CE. Tumors of the small intestine. N Engl J Med 1959; 260:397.

51. Garcia Marcilla JA, Sanchez Bueno F, Aguilar J, Parrilla Paricio P. Primary small bowel malignant tumors. Eur J Surg Oncol 1994; 20:630.

52. Michelassi F, Testa G, Pomidor WJ, et al. Adenocarcinoma complicating Crohn's disease. Dis Colon Rectum 1993; 36:654.

53. Lynch HT, Smyrk TC, Lynch PM, et al. Adenocarcinoma of the small bowel in lynch syndrome II. Cancer 1989; 64:2178.

54. MOERTEL CG, SAUER WG, DOCKERTY MB, BAGGENSTOSS AH. Life history of the carcinoid tumor of the small intestine. Cancer 1961; 14:901.

55. Saha S, Hoda S, Godfrey R, et al. Carcinoid tumors of the gastrointestinal tract: a 44-year experience. South Med J 1989; 82:1501.

56. Dabaja BS, Suki D, Pro B, et al. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer 2004; 101:518.

57. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg 2010; 199:797.

58. Ross RK, Hartnett NM, Bernstein L, Henderson BE. Epidemiology of adenocarcinomas of the small intestine: is bile a small bowel carcinogen? Br J Cancer 1991; 63:143.

59. Ribeiro MB, Greenstein AJ, Heimann TM, et al. Adenocarcinoma of the small intestine in Crohn's disease. Surg Gynecol Obstet 1991; 173:343.

60. Widmar M, Greenstein AJ, Sachar DB, et al. Small bowel adenocarcinoma in Crohn's disease. J Gastrointest Surg 2011; 15:797.

61. Palascak-Juif V, Bouvier AM, Cosnes J, et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. Inflamm Bowel Dis 2005; 11:828.

62. Howe JR, Karnell LH, Menck HR, Scott-Conner C. The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985-1995. Cancer 1999; 86:2693.

63. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017; 3:1335.

64. Massironi S, Campana D, Partelli S, et al. Heterogeneity of Duodenal Neuroendocrine

Tumors: An Italian Multi-center Experience. Ann Surg Oncol 2018; 25:3200.

65. Laskaratos FM, Rombouts K, Caplin M, et al. Neuroendocrine tumors and fibrosis: An unsolved mystery? Cancer 2017; 123:4770.
66. AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 7th ed, Edge, SB, Byrd, DR, Compton, CC, et al (Eds), Springer, New York 2010. p.181.
67. Niederle B, Pape UF, Costa F, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. Neuroendocrinology 2016; 103:125.
68. Bergsland EK, Woltering EA, Rindi G, et al. Neuroendocrine tumors of the duodenum and a mpulla of Vater. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.361.
69. Woltering EA, Bergsland EK, Beyer DT, et al. Neuroendocrine tumors of the jejunum and ile um. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.375. Corr ected at 4th printing, 2018.
70. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol 2017; 18:525.
71. Datta S, Williams N, Suortamo S, et al. Carcinoid syndrome from small bowel endocrine carcinoma in the absence of hepatic metastasis. Age Ageing 2011; 40:760.
72. Feldman JM, Jones RS. Carcinoid syndrome from gastrointestinal carcinoids without liver metastasis. Ann Surg 1982; 196:33.
73. Haq AU, Yook CR, Hiremath V, Kasimis BS. Carcinoid syndrome in the absence of liver metastasis: a case report and review of literature. Med Pediatr Oncol 1992; 20:221.
74. DAWSON IM, CORNES JS, MORSON BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg 1961; 49:80.
75. Cooper MJ, Williamson RC. Enteric adenoma and adenocarcinoma. World J Surg 1985; 9:914.
76. Sweetenham JW, Mead GM, Wright DH, et al. Involvement of the ileocaecal region by non-Hodgkin's lymphoma in adults: clinical features and results of treatment. Br J Cancer 1989; 60:366.
77. Koch P, del Valle F, Berdel WE, et al. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. J Clin Oncol 2001; 19:3861.
78. Domizio P, Owen RA, Shepherd NA, et al. Primary lymphoma of the small intestine. A clinicopathological study of 119 cases. Am J Surg Pathol 1993; 17:429.

79. Turowski GA, Basson MD. Primary malignant lymphoma of the intestine. Am J Surg 1995; 169:433.

80. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361.

81. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17:3835.

82. Isaacson PG. Gastrointestinal lymphoma. Hum Pathol 1994; 25:1020.

83. Devaney K, Jaffe ES. The surgical pathology of gastrointestinal Hodgkin's disease. Am J Clin Pathol 1991; 95:794.

84. Howe JR, Karnell LH, Scott-Conner C. Small bowel sarcoma: analysis of survival from the National Cancer Data Base. Ann Surg Oncol 2001; 8:496.

85. Shimizu N, Kuramoto S, Mimura T, et al. Leiomyosarcoma originating in Meckel's diverticulum: report of a case and a review of 59 cases in the English literature. Surg Today 1997; 27:546.

86. Miettinen M, Kopczynski J, Makhlouf HR, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. Am J Surg Pathol 2003; 27:625.

87. Blanchard DK, Budde JM, Hatch GF 3rd, et al. Tumors of the small intestine. World J Surg 2000; 24:421.

88. FARMER RG, HAWK WA. METASTATIC TUMORS OF THE SMALL BOWEL. Gastroenterology 1964; 47:496.

89. Kadakia SC, Parker A, Canales L. Metastatic tumors to the upper gastrointestinal tract: endoscopic experience. Am J Gastroenterol 1992; 87:1418.

90. Richie RE, Reynolds VH, Sawyers JL. Tumor metastases to the small bowel from extra-abdominal sites. South Med J 1973; 66:1383.

91. Elsayed AM, Albahra M, Nzeako UC, Sobin LH. Malignant melanomas in the small intestine: a study of 103 patients. Am J Gastroenterol 1996; 91:1001.

92. Lens M, Bataille V, Krivokapic Z. Melanoma of the small intestine. Lancet Oncol 2009; 10:516.

93. Kemp CD, Russell RT, Sharp KW. Resection of benign duodenal neoplasms. Am Surg 2007; 73:1086.

94. Witteman BJ, Janssens AR, Griffioen G, Lamers CB. Villous tumours of the duodenum. An analysis of the literature with emphasis on malignant transformation. Neth J Med 1993; 42:5.

95. Seifert E, Schulte F, Stolte M. Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. Am J Gastroenterol 1992; 87:37.

96. Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989; 2:783.

97. ASGE Standards of Practice Committee, Chathadi KV, Khashab MA, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc 2015; 82:773.

98. Apel D, Jakobs R, Weickert U, Riemann JF. High frequency of colorectal adenoma in patients with duodenal adenoma but without familial adenomatous polyposis. Gastrointest Endosc 2004; 60:397.

99. Schneider AR, Seifert H, Trojan J, et al. Frequency of colorectal polyps in patients with sporadic adenomas or adenocarcinomas of the papilla of vater--an age-matched, controlled study. Z Gastroenterol 2005; 43:1123.

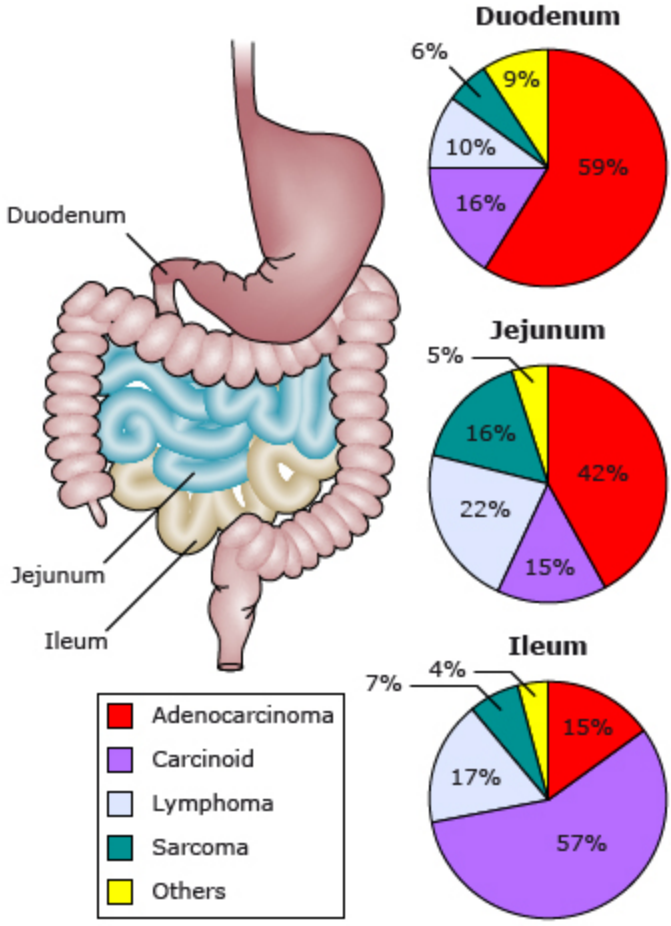
100. Murray MA, Zimmerman MJ, Ee HC. Sporadic duodenal adenoma is associated with colorectal neoplasia. Gut 2004; 53:261.

101. Dudiak KM, Johnson CD, Stephens DH. Primary tumors of the small intestine: CT evaluation. AJR Am J Roentgenol 1989; 152:995.

Topic 2517 Version 50.0

GRAPHICS

Proportion of histologic tumor subtypes found in the three anatomical segments of the small bowel from a combined analysis of registry-based data from three published series



Epidemiology of small bowel tumors from the NCDB (1985 to 2005) and United States SEER (1973 to 2005) cohorts, and the Connecticut Tumor Registry 1980 to 2000. The proportion of histological tumor subtypes found in the small bowel varies depending on the anatomic location of the small bowel.

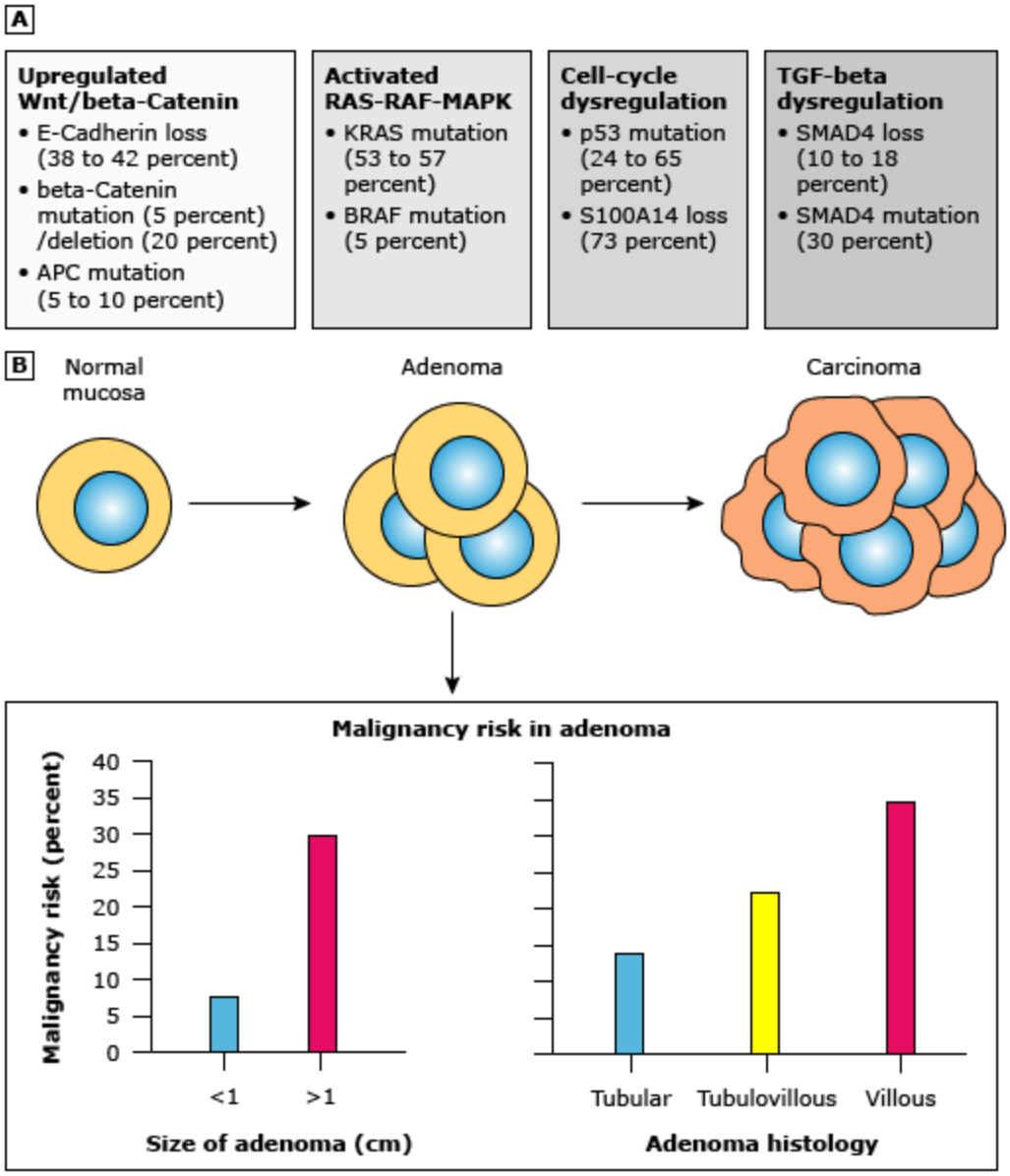
NCDB: National Cancer Data Base; SEER: Surveillance, Epidemiology, and End Results.

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Clinical Oncology. Raghav K, Overman MJ. Small bowel adenocarcinomas--existing evidence

and evolving paradigms. Nat Rev Clin Oncol 2013; 10:534. Copyright © 2013. www.nature.com/nrclinonc.

Graphic 109933 Version 1.0

The adenoma carcinoma sequence in small bowel adenocarcinomas

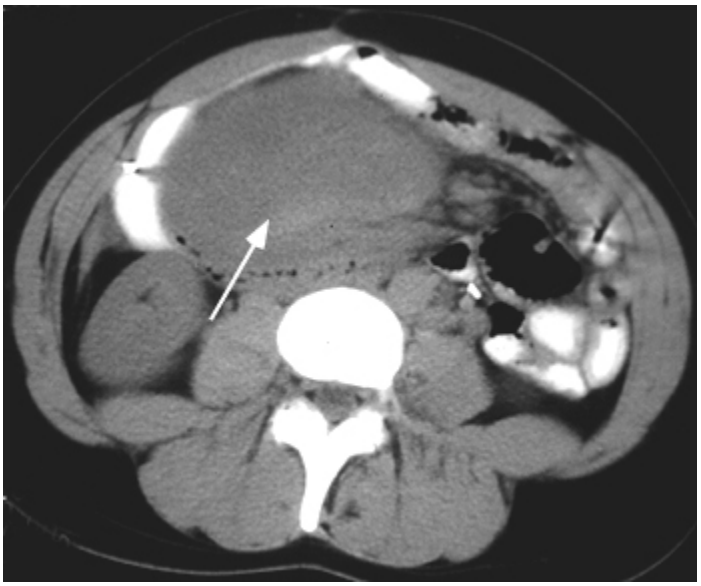


APC: adenomatous polyposis coli; TGF: transforming growth factor.

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Clinical Oncology. Raghav K, Overman MJ. Small bowel adenocarcinomas--existing evidence and evolving paradigms. Nat Rev Clin Oncol 2013; 10:534. Copyright © 2013. www.nature.com/nrclinonc.

Graphic 91173 Version 1.0

Intraabdominal desmoid tumor in familial polyposis

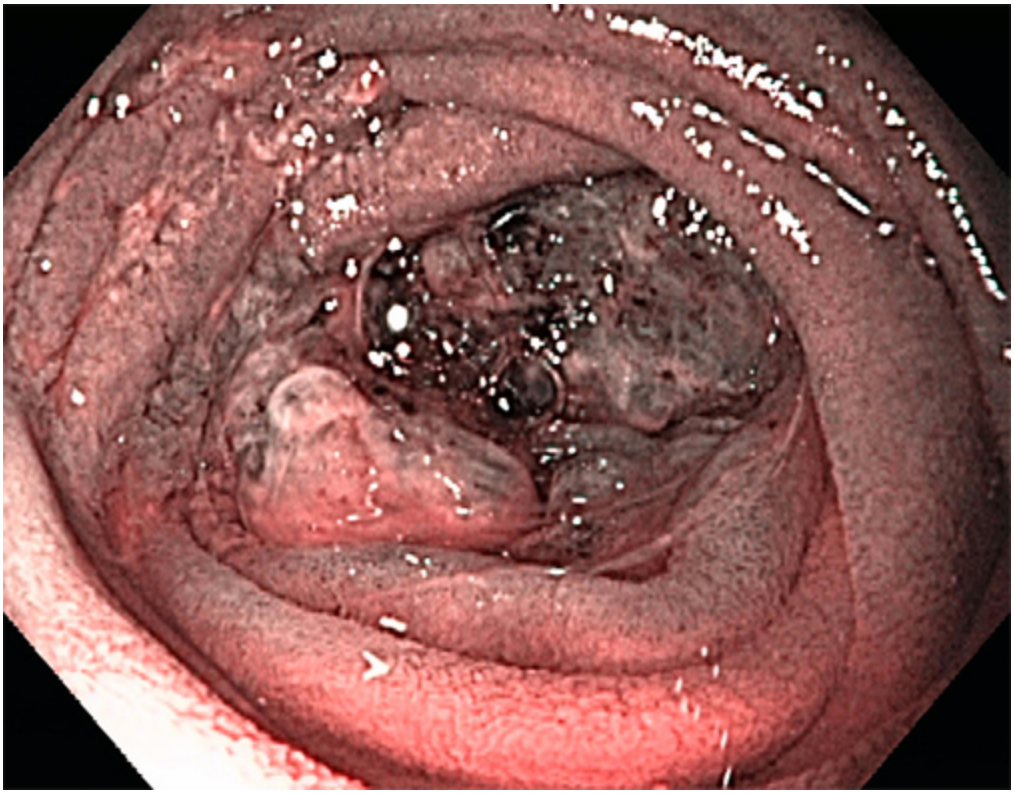


Computed tomography (CT) scan through the mid-abdomen demonstrates a large well-circumscribed soft tissue mass arising in the mesentery (arrow); the mass represented a desmoid tumor (aggressive fibromatosis).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 54879 Version 5.0

Duodenal adenocarcinoma as seen on upper endoscopy

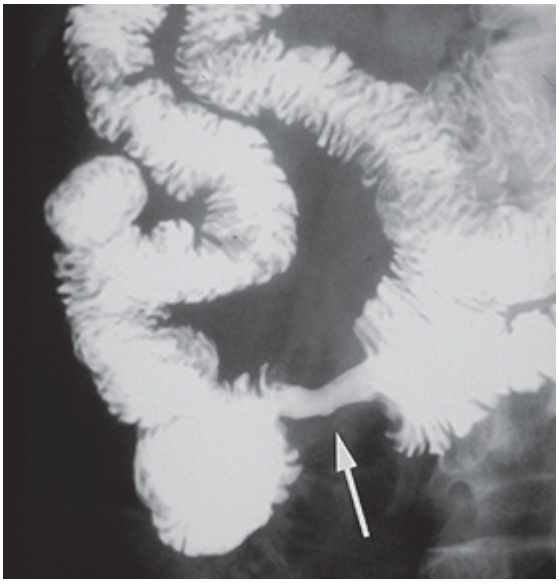


Irregular ulcerated mass in the third portion of the duodenum as seen on upper gastrointestinal endoscopy that was performed for work-up of iron deficiency anemia. Biopsy confirmed a moderately differentiated adenocarcinoma.

Courtesy of Michael J Overman, MD.

Graphic 62067 Version 2.0

Adenocarcinoma of the jejunum



Small bowel follow through examination demonstrates a circumferential apple-core lesion of the jejunum (arrow), producing distension of the proximal small bowel.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 58561 Version 3.0

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.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 110785 Version 9.0

2010 ENETS/WHO nomenclature and classification for neuroendocrine neoplasms arising in the gastrointestinal (GI) tract

Differentiation	Grade	Mitotic count*	Ki-67 index¶	Traditional	ENETS, WHO
Well differentiated	Low grade (G1)	<2 per 10 HPF	<3%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G1
	Intermediate grade (G2)	2 to 20 per 10 HPF	3 to 20%	Carcinoid, atypical carcinoidΔ, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, G3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, G3, large cell

ENETS: European Neuroendocrine Tumor Society; WHO: World Health Organization; HPF: high-power fields.

* Counted in 10 HPF; 10 HPF = 2 mm^2, at least 40 fields (at 400x magnification) evaluated in areas of highest mitotic density. Cut-offs per American Joint Commission on Cancer Staging Manual, 8th edition.

¶ Ki-67 index as assessed by MIB1 antibody staining: percent positive after count of 2000 cells in area of highest nuclear labeling. Cut-offs per American Joint Commission on Cancer Staging Manual, 8th edition.

Δ The term "atypical carcinoid" only applies to intermediate-grade neuroendocrine tumors of the lung.

Graphic 60365 Version 15.0

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

Carcinoid symptoms and their putative mediators

Organ	Symptom	Frequency (%)	Putative mediator
Skin	Flushing	85	Kinins, histamine, kallikreins, other
	Telangiectasia	25	
	Cyanosis	18	
	Pellagra	7	Excess tryptophan metabolism
Gastrointestinal tract	Diarrhea and cramping	75 to 85	Serotonin
Heart	Valvular lesions		Serotonin
	Right heart	40	
	Left heart	13	
Respiratory tract	Bronchoconstriction	19	Unknown

Graphic 63079 Version 9.0

Histologic grading scheme for gastrointestinal and pancreatic neuroendocrine neoplasms from the WHO and AJCC/UICC

Cellular pleomorphism per se is not a useful feature for grading NETs. The following grading scheme has been proposed for gastrointestinal NETs.	
Grade	**Definition**
GX	Grade cannot be assessed
G1	Mitotic count (per 10 HPF)* <2 and Ki-67 index (%)¶ <3
G2	Mitotic count (per 10 HPF) = 2 to 20 or Ki-67 index (%)¶ = 3 to 20
G3	Mitotic count (per 10 HPF) >20 or Ki-67 index (%)¶ >20

In cases of disparity between Ki-67 proliferative index and mitotic count, the result indicating a higher-grade tumor should be selected as the final grade. For example, a mitotic count of 1 per 10 HPF and a Ki-67 of 12% should be designated as a G2 NET.

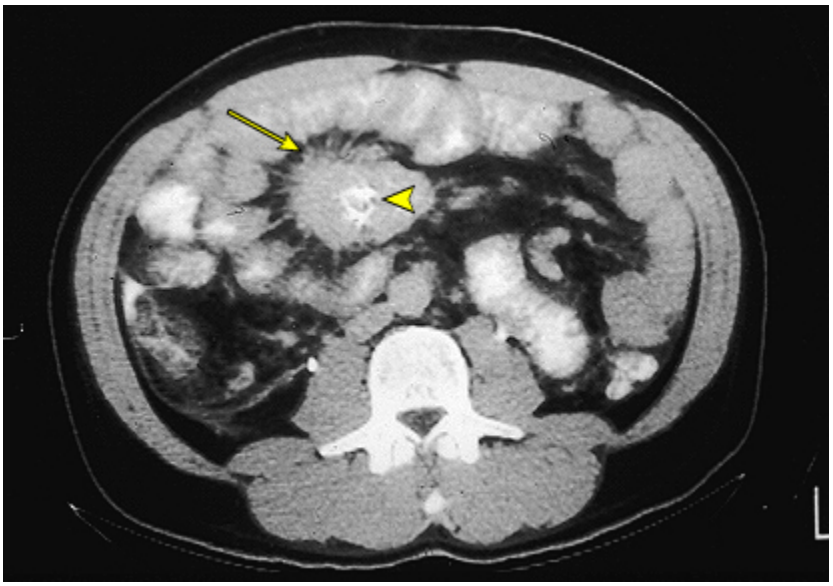
WHO: World Health Organization; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; NET: neuroendocrine tumor; HPF: high-power field.

* 10 HPF = 2 mm^2; at least 50 HPFs (at 40 times magnification) must be evaluated in areas of highest mitotic density in order to adhere to WHO 2010 and 2017 criteria.

¶ MIB1 antibody; % of 500 to 2000 tumor cells in areas of highest nuclear labeling.

Graphic 111125 Version 8.0

Radiographic features associated with small bowel neuroendocrine tumors

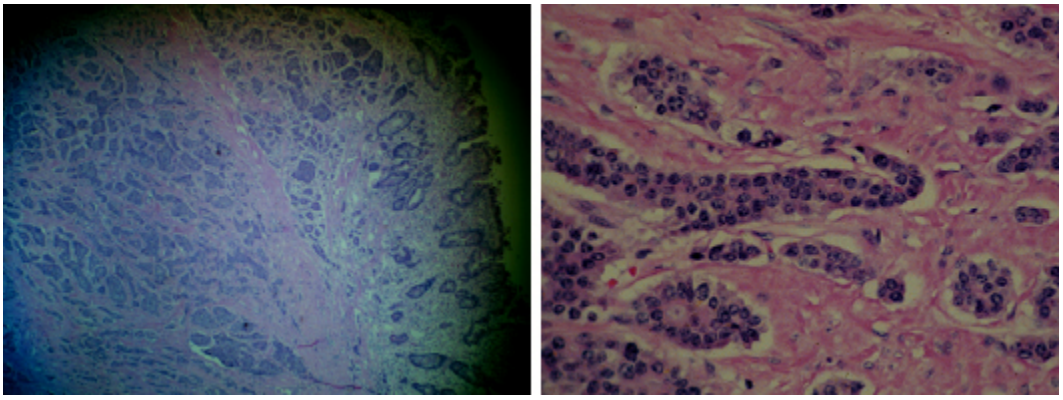


Computed tomography (CT) scan demonstrates a soft tissue mass containing coarse central calcifications (arrowhead) in the right lower quadrant. This neuroendocrine tumor is producing a characteristic desmoplastic response with spiculation of the adjacent mesenteric fat (arrow).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 78186 Version 5.0

Ileal carcinoid tumor

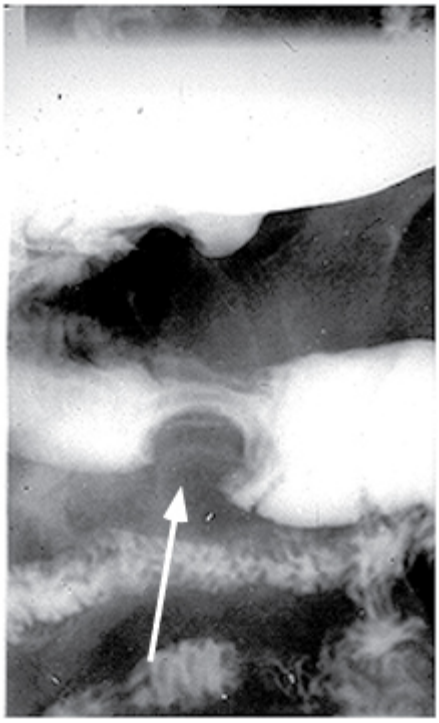


Low (left panel) and high power (right panel) histology of an ileal carcinoid tumor. The high power magnification demonstrates nests of uniform small cells and an absence of mitoses.

Courtesy of Dr. Saint Aufranc.

Graphic 77795 Version 1.0

Neuroendocrine tumor of the ileum, as seen on an upper gastrointestinal (UGI) study with small bowel follow through



Small bowel follow through examination shows a polypoid eccentric mass arising from the wall of the terminal ileum (arrow).

Courtesy of Norman Joffe, MD.

Graphic 60836 Version 3.0

Incidence of metastases related to the size of the primary gastroenteropancreatic neuroendocrine tumor

Tumor location and size, cm	Total patient numbers	Nodal metastases, number of patients (%)	Distant metastases, number of patients (%)
Small intestine			
≤1	43	5 (12)	2 (5)
1.1 to 1.9	83	58 (70)	16 (19)
≥2	59	50 (85)	28 (47)
Appendix			
≤1	431	0	0
1.1 to 1.9	53	4 (7.5)	2 (4)
≥2	33	11 (33)	4 (12)
Colon			
<2	11	2	2
≥2	42	26 (62)	17 (40)

Reproduced with permission from: Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. J Surg Oncol 2005; 89:151. Copyright © 2005 Wiley-Liss. Permission from John Wiley & Sons.

Graphic 82306 Version 5.0

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). Tumor ≤1 cm and confined within the sphincter of Oddi (ampullary tumors).
T2	Tumor invades the muscularis propria or is >1 cm (duodenal). 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): ▪ If the number of tumors is known, use T(#); eg, pT3(4) N0 M0. ▪ 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.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

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. ¶ *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.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

Graphic 111096 Version 9.0

Symptoms in gastrointestinal lymphoma according to involved site

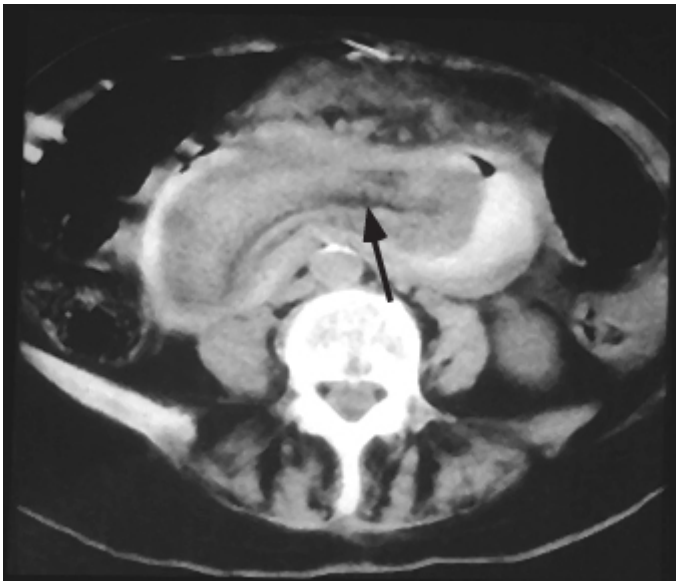
Symptom	Stomach (n=277)	Small bowel (n=32)	Ileocecal (n=26)	Multiple sites (n=24)
Pain	78	75	77	58
Loss of appetite	47	41	23	58
Weight loss	24	34	15	25
Bleeding	19	6	12	8
Vomiting	18	31	8	21
Night sweats	11	12	19	46
Diarrhea	4	12	19	29
Constipation	3	25	23	12
Fever	2	6	8	4
Perforation	2	9	-	-
Ileus	-	38	19	4
No symptoms	4	-	-	-

This table shows the percent of patients with the listed symptom at each of the four major sites of disease.

Data from Koch P, et al. J Clin Oncol 2001; 19:3861.

Graphic 68593 Version 2.0

Intussusception of small bowel lymphoma

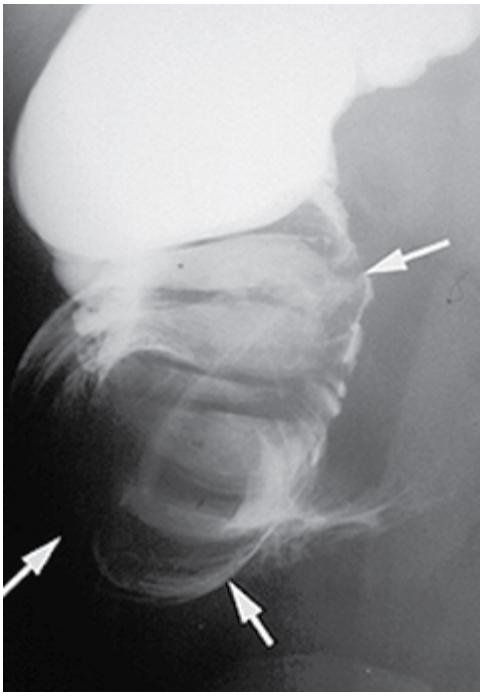


Computed tomography scan of the abdomen demonstrates a large mass in the lumen of a distended loop of small bowel. Note mesenteric fat in the center of this intraluminal mass (arrow).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 75825 Version 3.0

Intussusception of ileal lymphoma

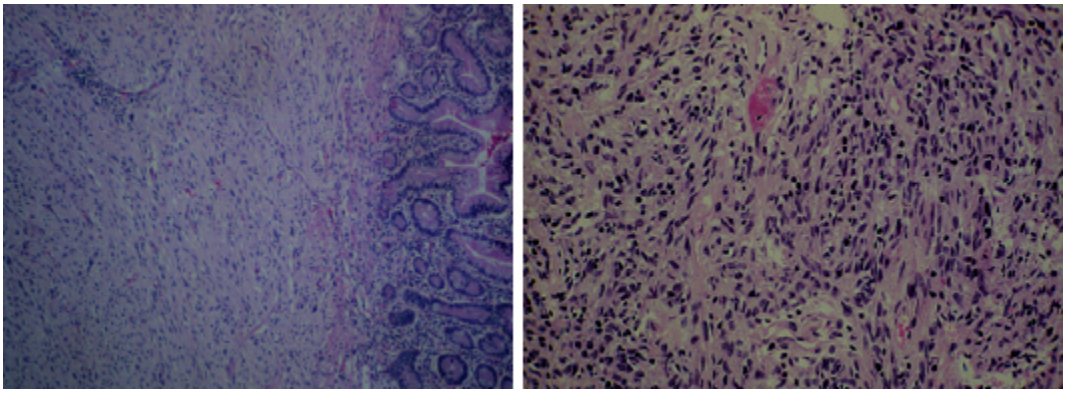


Barium enema shows a large soft tissue mass in the cecum (arrows) caused by intussusception of a lymphoma arising in the terminal ileum.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 64048 Version 2.0

Small intestinal leiomyosarcoma

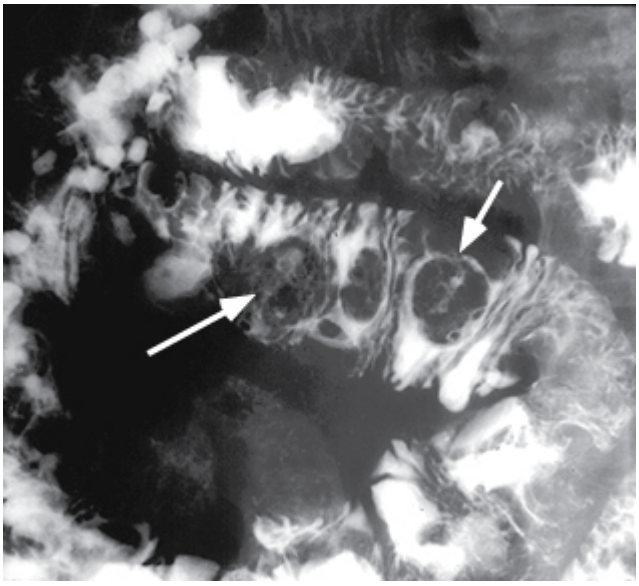


Low (left panel) and high power (right panel) images of a small bowel leiomyosarcoma. The high power view reveals pleiomorphic spindle cells with nuclear atypia, hypercellularity, and several mitotic figures.

Courtesy of Dr. Saint Aufranc.

Graphic 51522 Version 1.0

Melanoma of the small bowel

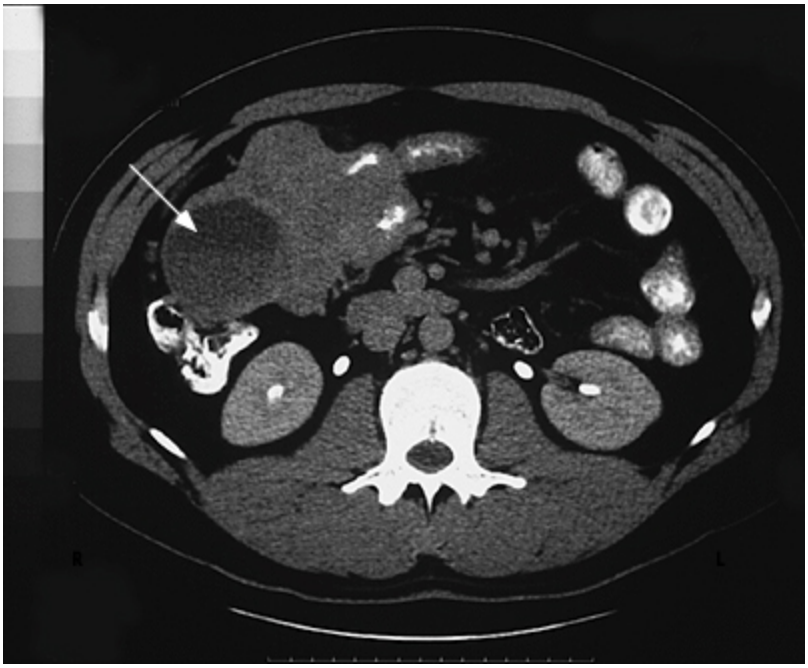


Small bowel follow through study shows multiple rounded, nodular filling defects in the wall of the small bowel (arrows). Multiple small bowel tumors may be seen in metastatic disease or in polyposis syndromes; the most common cause of small bowel metastases is melanoma.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 78537 Version 2.0

Small bowel leiomyoma

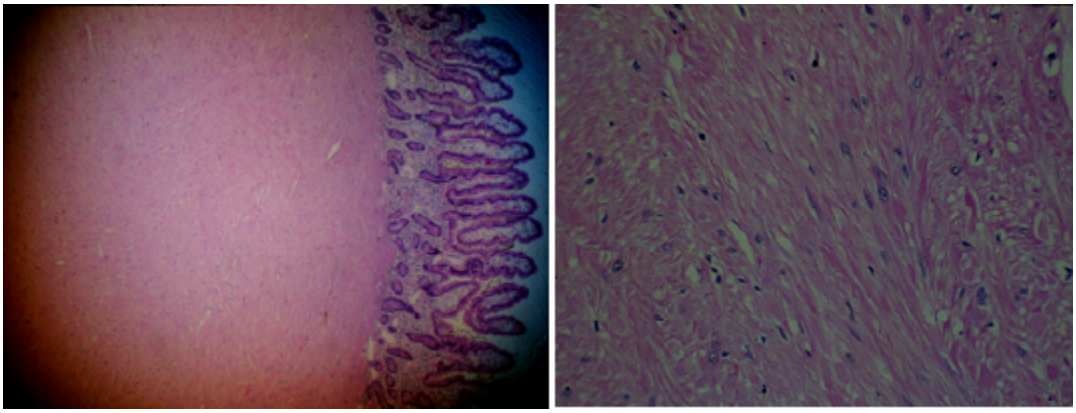


Preoperative CT scan shows a lobulated and cystic mass related to a loop of ileum. The small bowel leiomyoma has a focus of hemorrhage and necrosis (arrow).

CT: computed tomography.

Graphic 53060 Version 3.0

Small intestinal leiomyoma

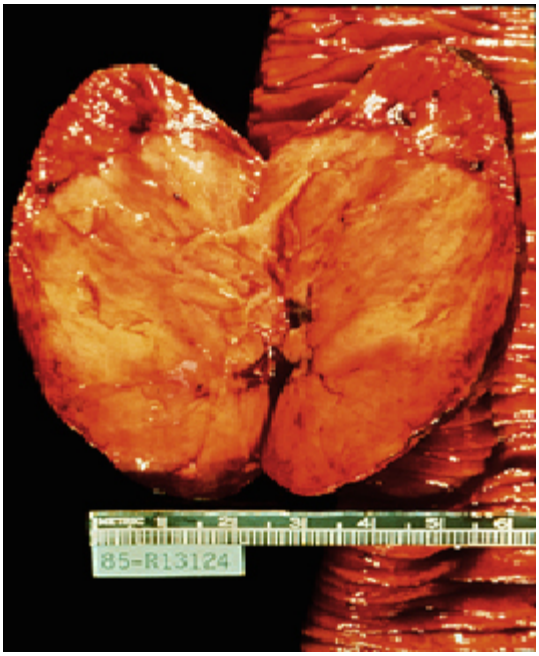


The left panel demonstrates the submucosal location of leiomyomas that arise in the small bowel. In the right panel, high power magnification reveals bland appearing spindle shaped cells and an absence of mitotic figures.

Courtesy of Dr. Saint Aufranc.

Graphic 72432 Version 1.0

Jejunal leiomyoma

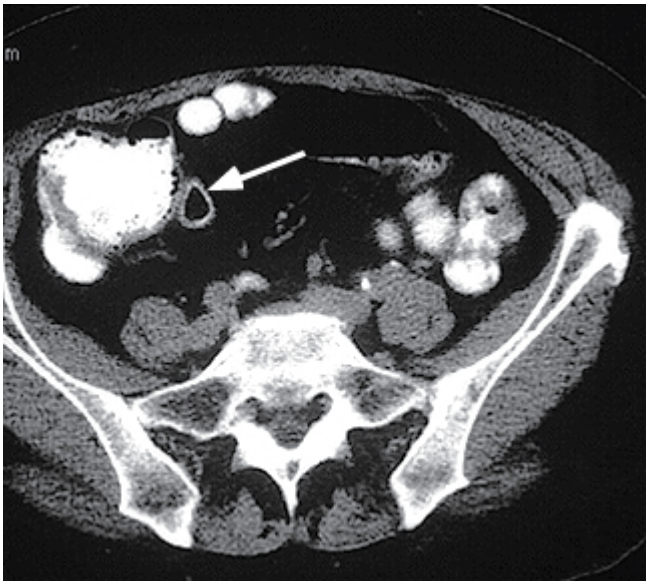


Surgical specimen of a large jejunal leiomyoma that caused a small bowel obstruction.

Courtesy of Robert Odze, MD.

Graphic 60327 Version 1.0

Lipoma of terminal ileum



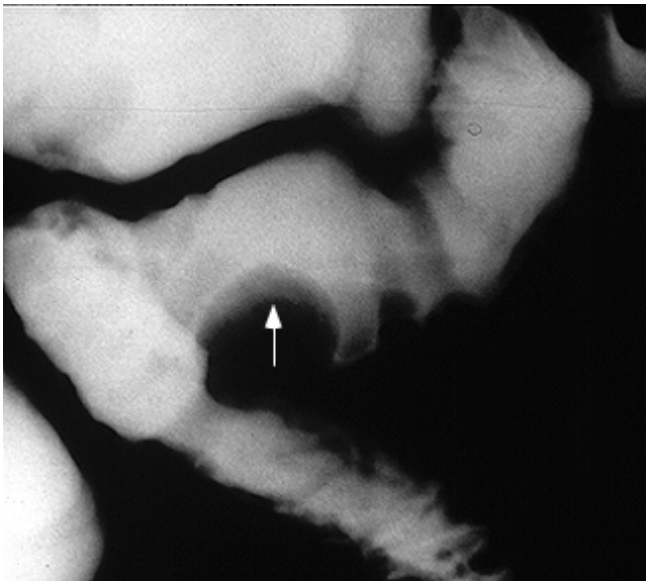
CT scan of the lower abdomen demonstrates a soft tissue mass of fat density in the lumen of the terminal ileum (arrow). These characteristics are diagnostic for a lipoma.

CT: computed tomography.

Courtesy of Norman Joffe, MD.

Graphic 68559 Version 3.0

Lipoma of the terminal ileum



Small bowel follow through examination demonstrates a smooth, well-circumscribed mass arising from the wall of the terminal ileum. The appearance is consistent with a benign mesenchymal tumor, such as a lipoma or a carcinoid tumor.

Courtesy of Norman Joffe, MD.

Graphic 80114 Version 2.0

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. **Hiroko Kunitake, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→