Review

Small bowel tumors

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SUMMARY

Small intestinal neoplasms are uncommonly encountered in clinical practice. Small intestinal neoplasms may occur sporadically, or in association with genetic diseases such as familial adenomatous polyposis coli or Peutz-Jeghers syndrome, or in association with chronic intestinal inflammatory disorders such as Crohn's disease or celiac sprue. Benign small intestinal tumors such as leiomyoma, lipoma, hamartoma or desmoid tumor, are usually asymptomatic but may present with intussception. Primary malignancies of the small intestine, including adenocarcinoma, leiomyosarcoma, carcinoid, and lymphoma, may present with intestinal obstruction, jaundice, bleeding, or pain. Extraintestinal neoplasms may involve the intestine via contiguous spread or peritoneal metastasis. Hematogenous metastases to the intestine from an extraintestinal primary are unusual and are most typical of melanoma. Because the small intestine is relatively inaccessible to routine endoscopy, diagnosis of small intestinal neoplasms is often delayed for months after onset of symptoms. When the diagnosis is suspected, enteroclysis is the most useful imaging study. Small bowel endoscopy (enteroscopy) is increasingly widely available and may permit earlier, non-operative diagnosis.

INTRODUCTION

Tumors of the small intestine present a unique challenge to the clinicians across medical specialties. Despite the fact that the small intestine represents approximately 75% of the total length of the gastrointestinal tract (GI) and more than 90% of the mucosal surface, and despite its anatomical location between two regions of high cancer risk, the small bowel rarely develops malignant tumors[1]. Fewer than 2% of all GI malignancies originate in the small bowel[2]. The age-adjusted incidence of small bowel malignancies is 1 per 100,000, with a prevalence of 0.6%[3].

Approximately 40 different histologic types of both benign and malignant small intestinal tumors have been identified[4]. Although 75% of the tumors found at autopsy are benign, most of the symptomatic lesions and tumors detected during surgery are malignant. An analysis of 10 series by Lee[5] showed that leiomyomas account for almost one fourth of all benign tumors of the small bowel. Other frequent benign tumors include lipomas, adenomas and hamar-tomas. Of the malignant tumors, approximately 30-50% are adenocarcinomas, 25-30% are carcinoids and 15-20% are lymphomas. The sites for the highest risk for malignant neoplasms are the duodenum for adenocarcinoma and the ileum for carcinoids and lymphomas[1].

This review is organized in two main parts. In the first part, we describe general aspects of the epidemiology, pathophysiology, clinical presentation and diagnostic work-up of small intestinal tumors. In the second part we discuss specific aspects of natural history and management for the most important of the individual tumors, which have been classified into benign, malignant, neuroendocrine, metastatic and tumors associated with certain chronic diseases or genetic abnormalities (Table 1).

PATHOGENETIC MECHANISMS IN SMALL INTESTINAL CARCINOGENESIS

The reason for the low incidence of carincogenesis in the small bowel, in comparison to the colon, remains

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Table 1. Classification of Small Intestinal Neoplasms

A.	**Benign**
	Leiomyoma
	Adenoma
	Lipoma
	Brunner's gland Hamartoma
	Hemangioma
	Nodular Lymphoid Hyperplasia
B.	**Malignant**
	Adenocarcinoma
	Lymphoma
	Leiomyosarcoma
	Other Sarcomas
	Ampullary adenocarinoma
C.	**Neuroendocrine**
	Carcinoid
	Ganglioneuroma
	Gastrinoma
	Somatostatinoma
	Vipoma
D.	**Conditions associated with SB tumors**
	Peutz-Jeghers syndrome
	Celiac disease
	IPSID
	Crohn's disease
	Neurofibromatosis
	AIDS
	Hereditary multiple polyposis syndromes
E.	**Metastatic**
	Malignant Melanoma
	Bronchogenic
	Breast CA

obscure. A number of mechanisms have been postulated to explain this decreased susceptibility for neoplastic transformation:

a) The liquid contents of the small bowel may cause less mucosal irritation than the more solid contents of the colon;

b) The relatively rapid transit of intestinal contents through the small bowel may provide shorter exposure of its mucosa to carcinogens;

c) The much lower bacterial load in the small bowel may result in decreased; conversion of bile acids into potential carcinogens by anaerobic microorganisms;

d) Benz(o)pyrene, a known carcinogen present in various foods, is converted in less toxic metabolites by benz(o)pyrene hydroxylase, which is present in much higher concentrations in the small intestine compared to the stomach and colon[7];

e) The increased lymphoid tissue with a high level of (secretory) IgA expression in the small bowel may be protective;

f) Direct exposure to various carcinogens may also be important. In one series, red meat and salt-cured foods were associated with increased risk while alcohol and smoking were not[8].

Certain hereditary syndromes are associated with an increased incidence of particular histologic types of small intestinal tumors. These include the Peutz-Jeghers syndrome (hamartomatous polyps occurring primarily in the jejunum and ileum), familial adenomatous polyposis and Gardner's syndrome (adenoma and adenocarcinoma) and von Recklingshausen's disease (paraganglioma). Desmoid tumors, which are often multiple, may be the primary manifestation of Gardner's syndrome in the small bowel[9].

Small intestinal inflammatory disorders that predispose to malignancy include Crohn's disease (adenocarcinoma), celiac disease (lymphoma and less frequently adenocarcinoma), and immunoproliferative disease (IPSID, diffuse intestinal lymphoma).

CLINICAL PRESENTATION

Small bowel tumors often present insidiously with nonspecific complaints such as intermittent abdominal pain, anemia, bleeding or obstruction. Consequently, they are often overlooked by the physician at initial presentation and the correct diagnosis is delayed. Differential diagnosis includes many more common causes of pain ranging from irritable bowel syndrome, acid peptic disease and cholelithiasis to diverticular disease and endometriosis. In a large series, mean time to diagnosis from the onset of the initial complaint in patients with small intestinal tumors was seven months[4]. Small bowel tumors commonly are found unexpectedly at surgery in patients presenting with small bowel obstruction. Benign small intestinal tumors usually remain aymptomatic and are discovered only at autopsy.

Patients with small intestinal tumors also may present with intermittent bowel obstruction, abdominal pain, intermittent gastrointestinal hemorrhage, or chronic anemia from occult GI blood loss. Gastric outlet obstruc-

tion can be the initial presentation with duodenal lesions. Intermittent obstruction and bleeding can occur as a result of intussusception, with lipoma being the most common cause of this complication. Desmoid tumors may grow intraluminally or extaluminally presenting as an obstruction or a palpable mass respectively. Hemangiomas are rare benign small bowel tumors that usually cause bleeding.

Malignant tumors are most likely to produce symptoms such as abdominal pain and weight loss. Adenocarcinomas represent 30% to 50% of small tumors[10], occurring in the sixth and seventh decades and with a slight male predominance. Adenocarcinomas are more common in the proximal small bowel with the most frequent being periampullary. Obstructive jaundice due to the obstruction of the distal common duct (CBD) outlet can be a presenting symptom (Table 2). Patients with Crohn's disease are an exception to the proximal location of adenocarcinoma; more than 75% of small bowel cancers in Crohn's disease are located in the ileum.

DIAGNOSTIC IMAGING

It is important to consider the possibility of a small bowel tumor in the setting of nonspecific abdominal complaints or chronic, unexplained iron deficiency anemia. The usual tests used for evaluation of abdominal complaints, including esophagogastroduodenoscopy, colonoscopy, small bowel series (also termed SBFT for "small bowel follow through") and abdominal ultrasound may be diagnostic, especially in advanced lesions, but they are relatively insensitive for early diagnosis of curable small intestinal malignancy. Excessive reliance on these studies can create a false sense of security. A delay in the diagnosis of small bowel tumors usually occurs while the patient is under active medical care, and is more likely to be caused by failure to order or misinterpretation of appropriate diagnostic testing, rather than a patient's failure to report symptoms[10].

Small bowel x-rays are currently the most widely used studies for diagnosis of focal small intestinal lesions. Plain abdominal radiographs may reveal obstruction, a calcified mass or evidence of hollow viscus perforation, but their overall yield in uncomplicated small bowel tumors is very low. CT is often used as a front line tool in the evaluation of abdominal complaints. The routine small bowel follow through (SBFT) is simple, inexpensive and non-invasive, but is relatively insensitive. Much more accurate information can be obtained using enteroclysis. In this double contrast X-ray study, the descending duodenum is first intubated. Barium and methylcellulose are then infused under pressure into the small intestine. This method produces distention of the bowel and allows the fluoroscopist to follow the movement of the contrast material through the gut. As compared to the traditional small bowel series, enteroclysis permits better visualization not only of the intestinal lumen but also of the mucosal surface. Transient delay in passage of contrast can identify areas of partial obstruction that are otherwise extremely difficult to locate. In one series, enteroclysis had a sensitivity of 90% for small bowel tumors, versus only 33% with SBFT[11].

Computed tomography (CT) can identify masses but is insensitive for diagnosis of small tumors and has a limited ability to differentiate between tumor types. Its greatest utility seems to be in the preoperative staging and evaluation of metastases[13-14]. However, in a recent report from Johns Hopkins Hospital, CT evaluation of small bowel neoplasms revealed certain characteristic features of some of these tumors, thus allowing for their differentiation[15]. Computerized tomographic (CT) enteroclysis, a combination of CT scan with barium infusion through a nasogastric (NG) tube, has been the subject of recent favorable reports from Europe[12] but remains an investigational tool at present.

Table 2. Clinical presentation of some selected small bowel neoplasms

Presenting Symptom / Sign	Most Likely SB Tumor
Jaundice + Melena	Ampullary Carcinoma
Flushing + Diarrhea	Carcinoid (metastatic)
Fever + Diarrhea + Weight Loss	Lymphoma
Intestinal Obstruction	Lipoma
Intussusception + Melanin Pigmentation	Peutz-Jeghers Syndrome
GI Bleeding	Leiomyoma
Perforation	Leiomyosarcoma/Lymphoma

Despite some earlier favorable reports, the utility of magnetic resonance imaging (MRI) and abdominal ultrasonography (US) in the diagnosis of small bowel tumors is very limited 16). Most investigators believe that the detection of small bowel lesions by these methods is usually serendipitous[13]. In balance, this is a rapidly evolving area of imaging with continuous improvement; thus, no definitive conclusions can be drawn. A recent report on the MR imaging of the small bowel, using the HASTE technique, is very promising[17].

Endoscopic ultrasonography or endoscopic ultrasound (EUS) has been the most recent addition to the armamentarium of diagnostic modalities for the examination of the small bowel. This new technological achievement not only provides high resolution imaging of the gastrointestinal wall and surrounding structures, but also allows interventional diagnostic and therapeutic procedures under real-time EUS guidance[18]. The ability of EUS in detecting and staging small bowel lesions appears to be most applicable to ampullary tumors. Two recent comparative prospective studies in 87 patients, showed that EUS is superior to both CT and MRI in detecting ampullary tumors and predicting vascular invasion[19-20]. Moreover, EUS is a great diagnostic tool in the evaluation of submucosal tumors such as stromal tumors, gastrinomas and carcinoids as well as vascular lesions.

SMALL BOWEL ENDOSCOPY

Small bowel endoscopy (SBE) or enteroscopy is a relatively recent development in gastrointestinal endoscopy. Although the first prototype instruments were developed almost 3 decades ago, the technology has really come of age in the last 3-5 years[21-22]. SBE is no longer considered "an esoteric and rather terrifying procedure performed by a tiny band of enthusiasts in showy endoscopy units"[23], but a credible diagnostic tool. Currently there are 3 major techniques available for the direct endoscopic examination of the small intestine: a) Push enteroscopy[24]; b) Sonde (from the French word meaning "to probe or sound to depths") enteroscopy[25], and c) Intraoperative or laparoscopically-assisted enteroscopy[27].

Recently Swain and his coworkers reported the development of a fourth modality, a swallowable video capsule (M2A), which transmits images from the small intestine[28]. This new wireless endoscopic technique allows the direct visual access to the entire GI tract, but currently is limited by its inability to produce continuous video images and by lack of external control over its position and orientation. A comparison of the various diagnostic modalities used in the evaluation of suspected small intestinal neoplasms is shown in Table 3.

Push enteroscopy can be used to examine the jejunum for about 40-60 cm beyond the ligament of Treitz. It differs from standard endoscopy in two major aspects: a) the instruments employed are longer (220-250 cm as compared to 120 cm), and b) an overtube is usually employed to prevent looping of the endoscope in the stomach. The overtubes are 60-100 cm long and can be placed at or beyond the pylorus. Fluoroscopy can be very helpful for the accurate placement and maneuvering of the scope and overtube. Like a standard enteroscope, the push enteroscope can be used to biopsy, excise or ablate tumors or bleeding lesions. Its major limitation is inability to visualize the distal jejunum and ileum.

Intraoperative endoscopy is a variant of push enteroscopy in which the instrument (usually a standard colonoscope or push enteroscope) is passed per os to the ligament of Treitz, then physically maneuvered through the bowel by the surgeon, who palpates the instrument through the intact bowel wall. Alternatively, a colonoscope may be placed into the rectum and manipulated retrograde through the small intestine by the surgeon. Intra-operative endoscopy permits rapid and complete endoscopic examination of the entire small bowel. When lesions are identified, their location is immediately apparent to the surgeon, who can identify the tip of the endoscope by its transillumination of the bowel. Multiple lesions (for example, polyps of the Peutz-Jeghers syndrome) may be marked individually by the surgeon with small sutures for subsequent resection upon conclusion of the enteroscopy. Although the applicability of this procedure is limited by the requirement for general anaesthesia and laparotomy, it can be invaluable in situations where other techniques have failed to identify pathology.

BENIGN TUMORS OF THE SMALL INTESTINE

Leiomyoma:

Leiomyomas are the most common symptomatic benign small bowel tumors, with a peak incidence between the ages of 50 and 60 years. The jejunum is the most frequent location of leiomyomas, followed by the ileum and the duodenum[29]. Leiomyomas are usually single, firm, grayish-white, well defined masses. They are often umbilicated with a central ulceration and are covered with normal epithelium. Four different growth patterns are

Table 3. Comparison of Diagnostic Modalities Used in the Evaluation of Suspected Small Intestinal Neoplasms

Diagnostic Test	Utility	Invasiveness	Cost
A. RADIOLOGY			
Abdominal X-rays (Plain)	±	±	±
SBFT	+	+	+
Enteroclysis	++	+	+
Ultrasound	+	0	+
CT Scan	++	+	++
MRI**	++	++	++
MRI + Enteroclysis	+++	++	++
Angiography	+	+++	+++
B. ENDOSCOPY			
EGD***	+	+	+
Push Enteroscopy	+++	++	++
Sonde Enteroscopy	++	++	++
Intraoperative Enteroscopy	++++	++++	++++
Colonoscopy with Ileoscopy	++	++	++
EUS****	ampullary lesions	++	+++
Pill video-camera	experimental	0	?
C. NUCLEAR MEDICINE			
Octreotide Scintigraphy	endocrine tumors	%/–	0
Gallium-67 Scan	±	±	
D. SURGERY			
Exploratory Laparotomy	++++	++++	++++
Laparoscopy	+++	+++	+++
E. PATHOLOGY			
Biopsy	+++	+++	0

* SBFT: Small Bowel (Series) Follow-Through

** MRI: Magnetic Resonance Imaging

*** EGD: Esophagogastroduodenoscopy

**** EUS: Endoscopic Ultrasonography

observed; intraluminal, intramural, extraluminal, and dumbbell-shaped[30]. Microscopically, leiomyomas consist of bundles of well-differentiated smooth muscle with no evidence of mitosis. The absence of mitosis is a critical parameter in ruling out malignancy (leiomyosarcoma).

In recent years, pathologists have begun to shift from the terms leiomyoma and leiomyosarcoma to the term *stromal tumor*. Thus, gastrointestinal stromal tumor (GIST) constitutes the current designation for the major subset of GI mesenchymal tumors and encompasses most tumors presently classified as GI smooth muscle tumors. A recent report from the Armed Forces Institute of Pathology (AFIP) has described the immunohistochemical spectrum of GIST at different sites of the GI tract and their differential diagnosis[31]. According to this study, GISTs typically express CD117 (KIT), whereas expression of alpha-smooth muscle actin (SMA) was most frequent in the GISTs of the small bowel. Thus, it appears that new molecular biology tests may soon become available for the precise characterization of these tumors and, more importantly, for the identification of malignant transformation, as indicated in the leiomyosarcoma segment of this paper.

Most leiomyomas remain asymptomatic and are found incidentally at autopsy. As these tumors tend to be highly vascular and ulcerate, GI bleeding is the most frequent presentation (65%), particularly in the duodenum. Bleeding can be precipitous with severe hemor-

rhage or occult, causing chronic iron deficiency anemia, with or without other symptoms. Obstruction from either intraluminal growth and compression or intussusception is the second most frequent presentation (25%). In a recent collective review of 1074 patients with leiomyomas, intussusception was a common finding, with ileal tumors occurring in about 40% of the patients[29]. Occasionally, the tumor may attain a size large enough to become palpable in an otherwise asymptomatic patient. Preoperative diagnosis of leiomyomas is difficult at best, partly owing to their rare occurrence and partly to the lack of any pathognomonic signs. Increased use of enteroclysis and enteroscopy can be expected to increase diagnostic yield.

Adenoma:

Adenomas are the most common asymptomatic benign small bowel tumors. Like their colon counterparts, three major histological types have been recognized: tubular, tubulovillous and villous. As with colonic adenomas, a villous component, atypia or large size increase the risk for malignancy. A large fraction of villous adenomas of the small intestine progress to malignancy[32]. In a retrospective analysis of 192 villous adenomas of the duodenum, the incidence of malignant changes at the time of presentation was 42%[33]. Because of their potential to undergo malignant transformation, these tumors should be removed or ablated endoscopically if this is technically feasible.

Most adenomas occur singly, although multiple adenomas may be found, especially in patients with one of the hereditary multiple polyposis syndromes. In general, endoscopic polypectomy for pedunculated tumors and surgical resection for large sessile lesions are appropriate. Prognosis is excellent for those tumors that lack malignant change, or in which malignancy is confined to superficial layers. It is recommended that all patients who have local tumor resection be surveyed with periodic endoscopies to assure complete tumor ablation and monitor for recurrence.

Lipoma:

Lipomas are the third most common benign tumors of the small intestine. They can be found anywhere, but are more commonly located distally. More than two thirds of lipomas remain asymptomatic and are found incidentally either at surgery or at autopsy. For those tumors that become symptomatic, intermittent intestinal obstruction and GI bleeding, often attributable to intussusception, are the cardinal manifestations.

Lipomas are easier to diagnose than other beign tumors of the small bowel. On barium studies, they present as very radiolucent, well-circumscribed, intramural lesions that change in shape and contour with compression or positional change. CT scan reveals a homogeneous mass with "fat" (low) attenuation[13]. Endoscopically, liponas appear as yellow-orange in color, smooth submucosal lesions with a positive "pillow" sign upon touch with the closed biopsy forceps. Lipomas have little or no malignant potential.

Brunner's Gland Hamartoma:

Brunner's gland hamartoma, also known as Brunner's gland adenoma or "Brunneroma", is an uncommon lesion of the proximal duodenum. These tumors are usually asymptomatic and diagnosed incidentally during an UGI endoscopy[34]. Occasionally, large hamartomas can lead to clinically significant symptomatology such as GI bleeding and obstruction[35-36]. The malignant potential for Brunner's gland hamartoma is virtually nil.

Hemangioma:

GI hemangiomas are relatively rare, comprising less than 0.05% of all intestinal neoplasms[37]. Occasionally they may be multiple and present with abdominal pain, bleeding and obstruction[38]. The diagnosis and endoscopic resection by intraoperative enteroscopy of a large bleeding hemangioma was recently described[39].

Intestinal Nodular Lymphoid Hyperplasia:

Nodular lymphoid hyperplasia of the small intestine is characterized by multiple large lymphoid follicles that give the appearance of submucosal masses. It is usually asymptomatic but it can be associated with diarrhea and malabsorption and, rarely, may lead to intussusception. It occurs more commonly in individuals with IgA deficiency or common variable immunodeficiency. Typically the process involves both distal jejunum and, ileum, and, rarely, the proximal colon[40]. Mild degrees of nodular lymphoid hyperplasia probably are of no clinical significance, but in some cases nodular lymphoid hyperplasia may presage the development of small intestinal lymphoma.

SMALL INTESTINAL MALIGNANCIES

Adenocarcinoma (non-ampullary):

Adenocarcinoma is the most common malignant tumor of the small intestine, accounting for approximately 30% to 50% of all malignant small bowel neoplasms[41-42]. The overwhelming majority of adenocarcinomas arise

from the proximal duodenum and jejunum, except in the setting of Crohn's disease. Peak incidence is in the seventh decade of life and there is a male preponderance[43].

Traditionally, adenocarcinoma of the small bowel has been considered to be similar in risk factors and geographic distribution to its colonic counterpart[44]. A recent multi-center European case-control study suggested an association with alcohol but not tobacco[45], as well as with certain occupations[46]. Other predisposing risk factors include: Crohn's disease[47], celiac disease[48], neurofibromatosis[49] and urinary diversion procedures such as ileal conduit[50-51]. The histogenesis of small bowel adenocarcinoma is probably analogous to the colonic adenoma-carcinoma sequence, through which the vast majority of colorectal cancers are thought to evolve[52]. Thus, the single, most important risk factor for small bowel adenocarcinoma is a preexisting adenoma, either single or multiple in association with one of the multiple polyposis syndromes[53]. It is noteworthy that more than 40% of patients with familial adenomatous polyposis have adenomatous polyps in the proximal small bowel and 5% develop invasive adenocarcinoma of the duodenum[54].

Adenocarcinomas, particularly those in the duodenum, become symptomatic much earlier than other small bowel tumors, thus allowing for earlier detection and therapeutic intervention. Despite this fact, most small bowel carcinomas are already metastatic at the time of diagnosis[55]. Unlike large bowel mucosa, small intestinal mucosa contains lymphatics that course through the villi extending near the luminal surface, and invasion of mucosal tumor into these lymphatics may account for this tendency to early metastasis.

The most common presentations of adenocarcinoma of the small bowel are obstruction, overt or occult GI bleeding, weight loss and jaundice. The diagnosis of proximal lesions with barium contrast studies and UGI endoscopy is straightforward. By contrast, diagnosis can be particularly difficult for adenocarcinomas of the ileum associated with Crohn's disease because the tumor can mimic an inflammatory exacerbation or a fibrous stricture[56]. The diagnosis of tumors located in other segments of the small bowel will typically require enteroclysis or enteroscopy. The presence of metastases can be evaluated with CT scan; in some instances MRI, EUS or angiography may also be useful.

Staging of the adenocarcinomas of the small bowel is carried out according to the TNM classification system. Surgery is the treatment of choice, and the only therapeutic modality with curative potential. Duodenal tumors may necessitate pancreaticoduodenectomy; in other locations, simple resection of the involved segment of bowel with accompanying mesentery and wide margins is sufficient. Neither chemotherapy nor radiotherapy has a proven role in the treatment of small bowel adenocarcinoma. Small adenocarcinomas, especially polypoid lesions with tumor confined to the mucosa and submucosa, sometimes can be cured by endoscopic resection (polypectomy or mucosectomy).

The prognosis of adenocarcinoma of the small intestine may be improving. In a recent landmark study conducted by the American College of Surgeons Commission on 5,000 small bowel adenocarcinomas, the overall 5-year disease-specific survival was 30.5%, with a median survival of 19.7 months[57]. Survival was lower in patients with duodenal tumors and in those who were older than 75 years, in part because of reluctance to pursue radical resection[58].

Ampullary adenocarcinoma:

The ampulla of Vater is the most common site of small bowel adenocarcinomas. In particular, the ampulla of Vater is the most common site of extracolonic malignancy in patients with familial adenomatous polyposis[59]; relative risk of ampullary carcinoma in patients with FAP is 100-200-fold greater than in the general population[60].

Lesions at this site often present early with bile duct obstruction and jaundice. Compared to more common malignancies that obstruct the bile duct, such as pancreatic adenocarcinoma or cholangiocarcinoma, ampullary adenocarcinomas are more indolent, more frequently resectable for cure, and have a much better prognosis. Failure to distinguish between these diagnostic possibilities may lead to inappropriate pursuit of palliative therapeutic strategies.

In addition to jaundice, symptoms associated with ampullary carcinoma include GI bleeding, obstruction, and abdominal discomfort. The concurrence of overt or occult GI bleeding and painless jaundice is suggestive of an ampullary carcinoma. Diagnosis usually can be established with barium contrast studies or endoscopy. Use of a side viewing duodenoscope is particularly helpful for examination and biopsy of the ampulla. EUS may be useful both for assessing depth of tumor invasion and for identifying nodal metastatic foci. Accurate staging is very important, as early lesions can be resected (typically by pancreaticoduodenectomy) with a subtantial probability of cure. In a recently published series from Johns Hopkins[61], among 120 patients with adenocarcinoma of the ampulla of Vater undergoing resection, reported five year

survival was 36%. Patients with unresectable lesions can be managed conservatively by palliative endoscopic interventions (i.e. laser photocoagulation, stent placement, etc).

Leiomyosarcoma:

Leiomyosarcoma is the fourth most common malignant tumor of the small intestine. The most frequent site of occurrence is the jejunum, followed by the ileum and duodenum. The peak incidence is in the sixth decade of life and there is a slight male preponderance. Similar to benign leiomyomas, leiomyosarcomas often grow to considerable size prior to the development of symptoms that lead to diagnostic studies. Recurrent melena or rectal bleeding from a central ulceration is not unusual. Most patients have a palpable mass at the time of diagnosis.

The differentiation of malignant from benign stromal tumors is often difficult. The old Evans criteria for malignancy are still in use in conjunction with the number of mitotic figures per high-power field (HPF). By consensus, most investigators accept that fewer than 2 mitosis per 10 HPFs (or 10 mitosis/50 HPFs) are strongly against leiomyosarcoma and are associated with an excellent prognosis. In contrast, tumors with a high number of mitoses correlate well with the presence of metastases and, thereby, poor 5-year survival (Table 4). Preliminary data from a recent pilot study suggest that the molecular determination of the malignant potential of leiomyomas will very soon become a powerful diagnostic tool. In this study, the lack of expression of the (-smooth muscle isoactin gene correlated 100% with malignancy in suspected leiomyosarcomas[62].

Surgical treatment is the only effective therapy for small bowel leiomyosarcomas. The operation usually involves the wide *en bloc* resection of the tumor including the adjacent mesentery. Neither chemotherapy nor radiation therapy have been shown to have a role in the management of leiomyosarcomas. Overall, prognosis is poor with a 5-year survival ranging from 28% to 33%[29]. However, when only high-grade lesions are considered, the median survival time from diagnosis is less than 18 months[63-64].

Lymphoma:

Lymphoma is the third most common primary malignant neoplasm of the small intestine accounting for 15-20% of all malignant small bowel tumors[65]. Non-Hodgkin's lymphoma of the gastrointestinal tract accounts for 5-20% of all non-Hodgkins lymphomas, and the gastrointestinal tract is the most common extranodal site of presentation of lymphoma[66-67]. The stomach is the most common primary site of origin in the digestive tract (more than two thirds) while the remaining cases are distributed evenly between small and large intestines[68].

The criteria for establishing the diagnosis of primary gastrointestinal lymphoma are:

a) Absence of palpable lymphadenopathy;

b) Normal peripheral blood smear and bone marrow biopsy;

c) Absence of mediastinal lymphadenopathy on chest x-ray;

d) Disease grossly confined to the affected small bowel segment, as confirmed by diagnostic imaging, endoscopy or laparotomy.

e) Regional lymphadenopathy only initially; and,

f) Absence of hepatic or splenic tumor involvement except via direct extension from primary bowel involvement.

Table 4. Mitotic Index vs Metastases and Outcome in GI Stromal Tumors (GIST)

Mitotic Index (N Mitoses / HPF*)	**Metastases (%)**	**5-Year Survival (%)**	**10-Year Survival (%)**
HIGH			
> 10/10 HPF	100	5	0
INTERMEDIATE TO HIGH			
> 5/10 HPF	15-25	25	13
LOW TO INTERMEDIATE			
1-5/HPF	5	75	38
LOW			
0-1/30HPF	< 1	100	100

* HPF: High Power Field

With the exception of T-cell lymphomas arising from the diseased small bowel in celiac sprue, almost all primary intestinal lymphomas are non-Hodgkin's B-cell lymphomas of intermediate or high malignancy[69]. The classification of gastrointestinal lymphoma is depicted in Table 5. It is important to distinguish primary small bowel lymphoma from immunoproliferative small intestinal disease (IPSID).

The usual clinical presentation includes intermittent abdominal pain, fatigue, diarrhea, weight loss and, occasionally fever. Less commonly, GI bleeding, obstruction or even perforation (up to 25%) may be the initial manifestations of primary intestinal lymphoma. At laparotomy, often performed as an emergency surgery, the lesions are usually large (three fourths of the lesions are larger than 5 cm) and may extend widely submucosally, with or without regional lymph node involvement[70].

Table 5. Classification of Primary Gastrointestinal (NHL) Lymphoma

B-Cell Lymphoma
Low grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)
High grade B-cell lymphoma of MALT, " low grade component
Mediterranean lymphoma (IPSID), low grade, mixed, or high grade
Malignant lymphoma, centrocytic
Burkitt-like lymphoma
Other forms of lymphoma corresponding to peripheral lymph node classification
T-Cell Lymphoma
Enteropathy-associated T-cell lymphoma (EATL)
Non-EATL

Traditionally, the Ann Arbor classification system[71], as modified by Musshoff[72] has been used for staging lymphomas. In the mid-1990s, at an international consensus workshop, Blackledge proposed a new classification and staging system for gastrointestinal lymphomas that was quickly adopted by most investigators in the field and is currently in widespread use[73]. Recently, this classification system has been superseded by a revised European-American Lymphoma classification, which includes entities such as T-cell lymphoma, maltoma and mantle-cell lymphoma[74]. Classification systems are summarized in Table 6. It remains to be seen whether the newer classification systems will prevail and prove to be better predictors of prognosis and response to therapy. These systems have some aspects in common, and each of the major staging systems in current use recognizes four major stages of primary small bowel lymphoma: stage I for local disease, II for regional involvement, and stages III and IV for advanced disease with metastases.

Table 6. A comparison of the three major staging settings of gastrointestinal lymphomas

Ann Arbor		Musshoff		Blackledge	
Stage	**Sites of Involvement**	**Stage**	**Sites of Involvement**	**Stage**	**Sites of Involvement**
I E	Single GI tumor focus without nodal involvemen	I E	Tumor confined to GI tract	I	Tumor confined to GI tract, no serosal penetration, non-contiguous foci
II E	GI tumor focus nodal involvement on one side of diaphragm	II E_1	Tumor with regional nodal involvement (i.e. celiac)	II II_1	Tumor with nodal involvement Regional nodes (gastric, mesenteric)
		II E_2	Tumor with extra-regional sub-diaphragmatic nodal involvement (i.e. para-aortic)	II_2	Extra-regional nodes (para-aortic, retrocaval)
III E	GI tumor focus, nodal involvement on both sides of diaphragm	III E	Tumor with nodal involvement on both sides of diaphragm	III E	Tumor with serosal invasion Adjacent structure involvement designating the actual site (i.e. stage II E pancreas, stage II E colon) Perforation and/or peritonitis
III ES	Spleen involvement				
IV E	GI tumor focus disseminated involvement of extra-lymphatic systems (i.e. bone marrow, liver)	IV E	Tumor with other extra-nodal documented involvement (i.e. bone marrow, liver)	IV	GI tumor focus, nodal involvement on both sides of diaphragm or other extra-nodal involvement (i.e. bone marrow)

The overall prognosis of the more advanced stages of primary small intestinal lymphoma is only fair, with an expected 5-year survival of 25% to 30%[75]. In general, predictors of poor prognosis include: stage greater than IIE_2, tumor size larger than 10 cm, immunoblastic histology, presence of aneuploidy, T-lymphocyte immunoperoxidase staining and clinical presentation with acute abdomen. In a retrospective analysis of 32 cases of PSBL treated with either radical surgery plus polychemotherapy (early stages IE and IIE) or systemic polychemotherapy alone (for advanced stages IIIE and IVE), the overall 5-year survival was 59%; more importantly, the relapse-free survival rate among the complete responders was 72%[76]. These results suggest that an aggressive multimodal therapeutic approach can improve outcome. In contrast to B-cell lymphomas, intestinal T-cell lymphomas carry a dismal prognosis. Domizio and coworkers[77] noted a 75% 5-year survival among their patients with B-cell intestinal lymphomas but only 25% in those with intestinal T-cell tumors.

Other less frequent forms of intestinal lymphomas include maltomas (MALT, mucosa-associated lymphoid tissue)[78,79] and primary macroglobulinemia of Waldenstrom, a similar entity to that of the stomach[80]. A full discussion of these lesions is beyond the scope of this review.

NEUROENDOCRINE TUMORS

Among neuroendocrine tumors arising in the GI tract, midgut argentaffin ECL (enterochromaffin-like) cell carcinoids[81], duodenal gastrin G-cell tumors[82] and rectal trabecular L cell carcinoids account for more than 80%[83]. The remainder includes other less common neuroendocrine tumors such as gangliocytic paragangliomas[84], somatostatinomas[85], vipomas[86] and schwannomas[87]. Carcinoid tumors have traditionally been classified according to their presumed derivation from different embryonic divisions of the gut (Table 7). In recent years, it has become apparent that the term "carcinoid" represents a wide spectrum of different neoplasms originating from a variety of different neuroendocrine cells. We will limit our discussion here to carcinoid tumors of the small intestine that secrete serotonin (5-hydroxytryptamine) or serotonin precursors.

The most credible and reliable statistical data have emerged from a landmark epidemiologic analysis of 8,305 cases of carcinoid tumors[88]. According to this study, the most frequent sites for carcinoids are the GI tract (73.5%) and the bronchopulmonary system (25%). Within the GI tract, most carcinoids occur in the small bowel (29%), appendix (19%), and rectum (12.5%). For all sites, age-adjusted incidence rates were highest in African American males (2.12 cases per 100,000 population per year), which is higher than the reported overall incidence in the U.S. (< 1.5 cases/100,000)[89]. The peak incidence of carcinoids is between the sixth and seventh decades of life.

Carcinoid lesions are characterized histologically by their affinity for silver stains, by general neuroendocrine markers (i.e. neuron-specific enolase, synaptophysin and chromogranin), or more specifically by immunocytochemistry, using antibodies against their specific cellular products (serotonin, histamine, neurotensin, dopamine and corticotropin)[90].

Clinical manifestations are often vague or absent and the tumors are detected incidentally at the time of surgery for other gastrointestinal diseases or evaluation of liver metastases. Some patients may develop abdominal pain, intussusception, intermittent obstruction, GI bleeding or a palpable mass. In approximately 10% of patients, the tumors secrete bioactive mediators and give rise to symptoms characteristic of the carcinoid syndrome: intermittent abdominal cramps, diarrhea, flushing, bronchospasm and cyanosis. The symptoms and course of carcinoid syndrome were summarized memorably in a limerick by Dr. William Bean:

This man was addicted to moanin',
Confusion, edema and groanin',
Intestinal rushes,
Great tricolored blushes,
And died from too much serotonin

Physical examination may reveal a loud holosystolic murmur in the tricuspid valve area. This is a nearly universal finding indicating tricuspid valve regurgitation, as a result of the retraction and fixation of its leaflets by plaquelike lesions (fibrous endocardial thickening) caused by carcinoid[91]. Contrary to some misconceptions, left-sided heart disease does occur in approximately 10% to 15% of patients with the carcinoid syndrome[92].

Standard imaging techniques, such as barium contrast studies, US, CT scan or even enteroclysis, rarely identify the primary tumor, thus making the preoperative diagnosis of small bowel carcinoid extremely difficult[93]. It is anticipated that improvement in the technology of direct enteroscopy will permit the preoperative diagnosis in a much larger number of patients. Other diagnostic tools include the use of various somatostatin-receptor radionuclide scans[95] and the measurement of carcinoid

Table 7. Characteristic Features of Carcinoid Tumors

Feature	Foregut	Midgut	Hindgut*
Anatomic Distribution	Bronchi	Small Bowel	Remainder
	Stomach/Duodenum	Cecum	of the Colon
	Pancreas	Ascending Colon	Rectum
Histology	Trabecular	Solid mass of cells	Mixed
Argyroplilic	+++	+	±
Argentaffin	%	+++	+
Primary Secreting Agents	5-HTP**	Serotonin	Rare
	Histamine		
Clinical Manifestations	Atypical Flushing	Flushing Diarrhea	None
Metastases	Bone	Liver	Bone
Carcinoid Syndrome	Atypical	Classical	Rare

* At least 100 cases of hindgut carcinoid have been reported in the genitourinary system

** 5-Hydroxy-tryptophan

products and their metabolites, such as serotonin and 5-hydroxy-indoloacetic acid (5HIAA). A diagnosis of the carcinoid syndrome is confirmed if the urinary 5-HIAA level is more then 10 mg in 24 hours[96].

The tendency of carcinoids for metastatic spread correlates with tumor size, and is substantially higher in tumors larger than 2.0 cm. Associated non-carcinoid tumors are found in approximately 17% of patients with small bowel carcinoid[88]. Lymph node metastases have been reported to be present in 20-45% of the cases. However, in the recent analysis of 8305 cases of carcinoid tumors mentioned earlier, non-localized lesions were found in 71% of these patients, thus providing the rationale for an extended resection including the adjacent lymph node drainage[94]. Carcinoid tumors of the appendix smaller than 1.0 cm rarely metastasize and a simple appendectomy is sufficient. Conversely, lesions larger than 2.0 cm should be treated with right hemicolectomy because of approximately 30% risk of lymph node involvement. The overall 5-year survival rate of carcinoid tumors of the small intestine is approximately 55%. This should be contrasted to the respective statistic for appendiceal carcinoid, which exceeds 85%[96].

Somatostatin analogues have a central role in both diagnosis and treatment of metastatic carcinoid tumors[89]. Somatostatin or its long-acting analogue octreotide act by binding to somatostatin receptors, which are expressed on more than 80% of carcinoid tumors[97]. In two large European studies, somatostatin scintigraphy detected carcinoid lesions with a sensitivity of 90%[98]. Octreotide is highly effective in relieving the symptoms of the carcinoid syndrome. In a pilot study, the administration of octreotide improved symptomatology in 90% of patients and decreased the urinary 5HIAA excretion in 80% of them[99]. Whether octreotide or the new long-acting analogue lanreotide can also induce regression of the tumors remains to be seen[100].

SYSTEMIC DISEASES ASSOCIATED WITH SMALL BOWEL NEOPLASMS

Peutz-Jeghers Syndrome:

Peutz-Jeghers syndrome (PJS) is a rare autosomal-dominant trait with variable incomplete penetrance[101]. PJS is characterized by hamartomatous polyposis of the GI tract, particularly in the small intestine, and focal melanin pigmentation of skin and mucous membranes[102]. The PJS polyp is an unusual type of polyp; its characteristic feature is a smooth muscle core arising from the muscularis mucosae and extending into the polyp[103]. The polyps are usually multiple and vary in size and shape; they are usually found in the small bowel and less frequently in the stomach and colon. Risks imposed by the presence of polyps in PJS patients include surgical emergencies such as small bowel intussusception and acute GI bleeding from the polyps.

As the polyps of PJS are hamartomas, and therefore non-neoplastic, the disease has traditionally been viewed as benign. However, PJS is clearly associated with an increased risk for small intestinal adenocarcinoma. Whether these malignancies originate from the typical hamartomatous PJS polyps or from coexisting adenomas is not clear. Some investigators believe that some of the hamartomatous polyps possess have malignant po-

tential and they have proposed a new concept, i.e. the sequence of hamartoma-adenoma-carcinoma. In addition to the GI malignancies, PJS patients have a propensity for extraintestinal malignancies, originating from the ovaries, uterus, breast, testis and head and neck. The relative risk of cancer in PJS is 18 times higher than that of the general population[104].

The PJS gene, designated as LKB1 gene on chromosome 19, was recently identified and encodes for the serine-threonine kinase STKII. It is thought to act under normal conditions as a tumor-suppresser gene[105]. In a series of elegant studies, among members of six generations from the original Dutch family with the PJS, Westerman and his coworkers[106] confirmed that the LKB1 gene is indeed the PJS gene and is involved in the PJS phenotype.

Treatment of PJS remains problematical, as polyps are widespread in the small bowel. In the past, patients undergoing laparotomy were subjected to resections of long segments of the small bowel in an effort to eradicate the polyps. The recurring need for operation and more resections sometimes resulted in short bowel syndrome. Currently, the trend is to limit intestinal resection to the necessary minimum. The advent of enteroscopy has revolutionized management, permitting preoperative detection of the polyps and offering a non-operative approach to polyp clearance, thereby reducing the need for intestinal resection[107,108].

Celiac Disease:

Although the association of intestinal lymphoma with celiac disease has been known for almost 40 years, it was not until 1985 that was characterized as a T-cell lymphoma[109]. This enteropathy-associated T-cell lymphoma (EATL) is commonly accompanied by a non-specific mucosal ulceration, similar to that seen in another complication of celiac disease, "ulcerative jejunitis". EATL usually presents in the fifth decade of life as a clinical relapse of previously diagnosed celiac disease. Thus, the presence of symptoms refractory to gluten withdrawal in a patient with celiac disease should lead the clinician to suspect EATL. Chronic ulcerative enteritis and EATL may be parts of a continuous disease spectrum[110]. This concept was recently reaffirmed in an important study of 21 patients with refractory celiac disease[111]. Approximately three fourths of these patients had immunophenotypically aberrant clonal intra-epithelial (IEL) T-cell populations and a characteristic HLA (DQW2) phenotype. It is anticipated that these findings may provide new insignts into the etiological factors that trigger the malignant transformation occurring in celiac disease.

Immuno-Proliferative Small Intestinal Disease (IPSID):

IPSID (also known as alpha-chain disease, Mediterranean lymphoma, or diffuse small intestinal lymphoma) is a special form of mucosa-associated lymphoid tissue (MALT) type lymphoma. It is prevalent in impoverished parts of the world such as the Middle East, Africa, Southeast Asia and South and Central America[112]. It is virtually unknown in the industrialized world except among immigrants from the developing countries. Most patients are young and there is no gender preference[113]. Poor standards of hygiene and endemic parasitic and other enteric infections are characteristic of the geographic regions in which IPSID is common[114]. For this reason, it is widely believed that microbial or parasitic colonization of the small bowel is of major etiologic significance[115]. The prompt response of early stages of IPSID to antibiotic therapy provides the strongest indirect supportive evidence for this theory.

IPSID is characterized by an intense lymphoplasmatocytic infiltration of the lamina propria and, sometimes, of the regional lymph nodes of the proximal small intestine[116]. The proliferating cells are IgA-secreting B lymphocytes. The "-heavy chain paraprotein that is detectable in the serum of 20-70% of these patients, usually during the early stages of the disease, derives from an expanded abnormal clone of these lymphocytes[117]. The lymphoma is usually of the immunoblastic variety[118].

Patient with IPSID usually present with chronic diarrhea, malabsorption syndrome, weight loss, abdominal pain, clubbing and growth retardation of months' to years' duration. IPSID frequently involves the upper jejunum and distal duodenum but occasionally the ileum may also be affected[119]. Barium contrast examination of the small bowel shows diffuse dilation of the small intestine with thickened mucosal folds and spiculated fold edges, similar to the edges of a postal stamp[120]. Enteroscopy reveals thickened, edematous and nodular mucosal folds, ulcerations and/or submucosal infiltration. The intestine is hypomotile and nondistensible[121]. Bacterial overgrowth in the small intestine and parasites, such as *Giardia* are common. The characteristic laboratory abnormality in IPSID is alpha-chain protein, a paraprotein of 29-34 kD MW[122] produced by neoplastic clones of IgA plasma cells[123]. The cardinal differences between IPSID and PSBL are shown in Table 8.

Since the original description of IPSID, classification and staging have undergone continuous changes and

adjustments and are still evolving. Of the three existing systems of pathologic classification and staging of IPSID[124-126], the scheme proposed by Galian et al[126] has prevailed. According to this system, IPSID has 3 different stages A-C, corresponding to early-benign, intermediate-premalignant and late-malignant stage. Currently, there is a lack of consensus regarding the optimal therapeutic strategies for IPSID[127]. By and large, treatment is usually tailored according to the stage of the disease. Consequently, antibiotic therapy (usually with tetracyclines) should be the first line of treatment in early-benign, stage A disease[128]. Indeed, several clinical trials have shown that antibiotic therapy results in a 70% complete response. For the nonresponders and for those with intermediate (B) or late (C) stages of disease, total abdominal radiation or, more frequently, combination chemotherapy is recommended[129].

Overall 5-year survival rates for patients with IPSID undergoing treatment have been about 75%. In a recent report[130] of 23 patients with IPSID, tetracycline alone yielded a 71% complete response in stage A patients while COPP regimen achieved complete response in 69% of patients with advanced (B and C) stages of the disease. The overall 5-year survival for the entire group was 70% and the 5-year disease-free survival for patients with complete response was 75%. Thus, combination chemotherapy such as COPP is a good alternative as a first-line treatment for patients with stage B or C IPSID-related low-grade lymphoma. Interestingly enough, the eradication of *Helicobacter pylori (Hp)* infection has been reported to lead to complete remission of IPSID[131], thus supporting the theory that a microbial pathogen may be an etiologic factor.

Crohn's Disease:

Patients with inflammatory bowel disease (IBD), especially those with ulcerative colitis, are at increased risk for developing cancer of the GI tract, particularly colorectal cancer[132]. In contrast, the risk for the development of malignancy in Crohn's disease is not as well defined[133]. The risk for the development of small intestinal (ileal) adenocarcinoma is greater in patients with Crohn's disease than in the general population, although the magnitude of this increased risk is unknown[134]. Several risk

Table 8. Clinical and Pathological Features of PSBL and IPSID-Related Lymphoma

Feature	PSBL	IPSID - Related
Epidemiological Data		
Median age (yrs)	40	25
Gender	Slight male predominance	Primarily male
Geographic distribution	Industrialized world	Developing world
Clinical Picture		
	Abdominal pain	Abdominal pain
	Palpable abdominal mass	Chronic diarrhea
	GI Bleeding	Malabsorption
	Intestinal obstruction	Severe weight loss
	Intestinal perforation	Ankle edeme
		Clubbing
		Growth retardation
		Paraprotein (∀-CP)
Pathology		
Cell type	Majority: B-cell; Celiac disease: T-cell	B-cell
Macroscopic	Localized tumors	Diffuse, longer bowel segments
Distribution	Mainly ileum	Mainly duodenum-jejunum
Microscopic	Follicles, Centrocyte-like cells (cleaved)	Dense mucosal infiltrate of
	Plasma cells, Cytologic monotony	plasmacytic/lymphoid cells,
Spread	Late and indolent	from low to high grade malignancy
	To spleen, liver and extra-abdominal nodes	To adjacent organs;
		Rare liver/spleen involvement

factors have been identified in patients with Crohn's disease who develop adenocarcinoma of the small bowel: gender, duration of disease (Crohn's), fistulization and, the presence of surgically created "blind" excluded loops of intestines. Likewise, the incidence of colorectal carcinoma in Crohn's disease is increased from 5-fold to 20-fold, with the right side of the colon being the most commonly affected. Until recently, most of the literature, pertaining to the association of Crohn's disease with malignant neoplasms of the small intestine, has reported consistently on the development of adenocarcinoma. In recent years, it has become apparent that the risk of lymphoma (NHL) in patients with Crohn's disease is also increased[137].

Other syndromes and/or conditions associated with small intestinal neoplasms include: Neurofibromatosis-1 (vov Recklingshausen's disease)[138], Acquired Immune Deficiency Syndrome (AIDS)[139], familial adenomatous polyposis (FAP)[140], Gardner's syndrome[141], Turcot's syndrome[142], Cronkhite-Canada syndrome[143], Cowden disease[144] and certain urological procedures, such as ileal conduit of ileocystoplasty[51].

METASTATIC NEOPLASMS

Secondary neoplastic involvement of the intestine is more frequent than primary small intestinal neoplasia. Extrinsic tumors may involve the gut by hematogenous metastasis, by direct invasion or by intraperitoneal seeding. Primary tumors of the colon, ovary, uterus and stomach usually involve the small bowel either by direct invasion or by intraperitoneal spread, whereas primaries from breast, lung[145] and melanoma metastasize to the small bowel hematogenously.

Melanoma is the extraintestinal malignancy with the greatest predilection to metastasize to the bowel. In the gastrointestinal tract, the small bowel is the most frequent site of metastasis of melanoma, mainly due to its rich blood supply. In a recent series of metastatic melanoma of the GI tract, the metastases were the presenting sign leading to diagnosis of melanoma in 50%[146]. Occasionally melanoma can also arise de novo as a primary enteric neoplasm from the mucosal epithelial lining of the small intestine[147]. A recent retrospective study from AFIP among 103 cases of malignant melanoma (77 surgical resections and 26 autopsies) concluded that small bowel involvement by melanoma, even in the absence of a known primary, is usually metastatic[148]. Despite some anecdotal reports[149] of prolonged survival after resection of small bowel melanoma its overall prognosis remains extremely poor. However, aggressive resection in cases without a known primary site may improve quality of life, and occasional long-term survival has been recorded.

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