Tumors of the Stomach & Small Intestine

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ESSENTIALS OF DIAGNOSIS

- *Common gastric and small intestinal malignancies include adenocarcinoma, lymphoma, metastatic carcinoma, gastrointestinal stromal tumors, and carcinoid. These must be differentiated from benign ulcerative lesions and polyps by endoscopic or surgical biopsy.*
- *Symptoms and signs include dyspepsia, weight loss, obstructive symptoms, and evidence of intestinal blood loss or iron deficiency anemia.*
- *Diagnosis of early stage gastric cancer requires a high index of suspicion for patients who are at increased risk, for example, new symptoms in patients aged over 40–45 years, history of prior gastric surgery, prior history of pernicious anemia, celiac sprue, immunodeficiency, or gastric polyps. Diagnosis requires referral for endoscopy and/or barium radiologic exams.*
- *Diagnosis of small bowel tumors often requires a barium enteroclysis examination performed by an experienced radiologist or endoscopy using small bowel enteroscopes.*

General Considerations

The stomach and less frequently the small intestine give rise to a variety of benign and malignant tumors (Table 24–1). In 5000 endoscopic examinations of the stomach conducted over a 7-year period at the University of Chicago, approximately 119 gastric malignancies (2.4%) and 125 benign gastric polyps (2.5%) were diagnosed. The most frequent gastric malignancy is adenocarcinoma, followed by primary gastric lymphoma, metastatic carcinoma, and less frequently leiomyosarcoma, carcinoid, and Kaposi's sarcoma. These present as ulcerated or polypoid lesions that must be differentiated from benign tumors by endoscopic or operative biopsies.

Gastric adenocarcinoma is the second most common malignancy worldwide. Gastric cancer is particularly common in Japan, China, Korea, Taiwan, Eastern Europe and countries of the former Soviet Union, Costa Rica, and South America. In Japan, the gastric cancer incidence is 100 per 100,000 persons and is the leading cause of cancer deaths. In the United States, the overall annual incidence of gastric cancer has declined from 33 cases per 100,000 population in 1935 to less than 6 cases per 100,000 in the 1990s. In the United States, it is estimated that 33,800 new cases of gastric cancer and 25,100 gastric cancer deaths occurred in the year 2000. Gastric cancer is currently the seventh leading cause of death due to malignancy among males and the eleventh among females in the United States. In contrast, the incidence of adenocarcinoma of the gastric cardia and gastroesophageal junction has been increasing in both the United States and Europe over the past 15 years.

Lymphoma is the second most common malignancy encountered in the stomach. Primary gastric lymphomas account for 3–5% of gastric neoplasms. The large majority of these lymphomas are B cell non-Hodgkin's lymphomas of the diffuse, large cell type. Gastric lymphoma is the most common extranodal lymphoma, accounting for 20–24% of primary extranodal lymphomas.

Less frequent primary gastric malignancies include carcinoid tumors and gastrointestinal stromal cell tumors (GISTs). The occurrence of carcinoids in the stomach is rare; approximately 95% of all carcinoid tumors occur in the rectum, appendix, and small intestine. GISTs represent the largest category of nonepithelial neoplasms of the gastrointestinal tract. They arise from the neoplastic degeneration of primitive mesenchymal cells and demonstrate considerable variability in their differentiation pathways. GISTs can be divided into several categories, including leiomyomas, schwannomas, and less differentiated tumors referred to as GIST. The GIST family may include most tumors labeled as leiomyomas, cellular leiomyoma, leiomyoblastomas, myofibroblastic tumors, and leiomyosarcomas. GISTs can occur in all segments of the intestine, with approximately 60% occuring in the stomach, 30% in

Table 24–1. Tumors of the stomach and small intestine.

Tumors	Percentage of Total	Benign Polyps	Percentage of Total
Gastric	**Endoscopic series**		**Endoscopic series**
Adenocarcinoma	86	Hyperplastic	71
Lymphoma	8	Adenomatous	11
Metastatic carcinoma	4	Leiomyoma	6
Leiomyosarcoma	<2	Pancreatic rest	<2
Carcinoid	<2	Myoepithelial hamartoma	<2
Kaposi's sarcoma		Peutz-Jeghers hamartoma, eosinophilic granuloma, no histologic diagnosis, neurogenic tumors, lipoma	5
Small intestine	**Surgical series**		**Surgical series**
Adenocarcinoma	29–40	Ademomas (polypoid, Brunner gland, islet cell)	25–38
Carcinoid	29–49	Leiomyoma	35
Leiomyosarcoma	15–22	Lipoma	4–20
Lymphoma	4–11	Hamartomas, fibromas, neurogenic	
Metastatic carcinoma		Angiomas, myxomas, other rare types	
Kaposi's sarcoma		Pseudotumors, lymphoid hyperplasia, hyperplastic inflammatory, pancreatic rests, Brunner gland hyperplasia, amyloidosis, endometrioma	

the small intestine, and 10% in the esophagus and colon. The clinical course of GISTs is heterogeneous and not easily predicted by standard clinicopathologic criteria. The most important prognostic features are size >5 cm, tumor necrosis, mitotic count >1 to 5 mitoses per 10 high power fields, and the presence of *c-kit* gene mutation.

Overall, tumors of the small intestine account for only 1–2% of all gastrointestinal malignancies. During a 20-year period at the Case Western Reserve University, 64 patients underwent surgical resection for primary small bowel tumors; of these 38 (59%) were malignant and 26 (41%) were benign. The relative frequencies of different histologic types of small bowel tumors are listed in Table 24–1. The majority of small bowel adenocarcinomas and leiomyosarcomas occur in the duodenum and jejunum. In contrast, the majority of small bowel carcinoids and lymphomas occur in the ileum.

Pathophysiology

Several case–control studies have suggested an association between *Helicobacter pylori* infection and gastric cancer, including gastric lymphomas and both intestinal and diffuse types of adenocarcinoma. A recent long-term, prospective study of 1246 patients with *H pylori* infection and 280 patients without *H pylori* infection in Japan was reported by Uemura et al. After a mean follow-up period of 7.8 years, gastric cancer was diagnosed in 2.9% of the infected patients and in none of the uninfected patients. Among the patients with *H pylori* infection, those with severe gastric atrophy, corpus-predominant gastritis, and intestinal metaplasia were at significantly higher risk for developing cancer.

The development of chronic atrophic gastritis in the corpus or gastric body and intestinal metaplasia leads to impaired gastric acid secretion, imbalanced cellular proliferation and apoptosis, and decreased gastric mucin synthesis. These histologic changes progress over long periods of time, and can eventually lead to the development of foci of dysplasia and cancer. Because only a small proportion of individuals infected with *H pylori* subsequently develop dysplasia or cancer, other carcinogenic factors are necessary. Numerous epidemiologic studies have identified other potential contributing factors for the development of gastric cancer. These include diets with low fat and protein intake, low vitamin

A and C intake, high intake of salted meat and fish, and high intake of nitrates. Low socioeconomic status is associated with increased cancer risk, which may be explained by poor food preparation, lack of refrigeration, and increased *H pylori* infection rates. Smoking increases the risk of gastric cancer, however alcohol intake does not. Investigators have speculated that the most important scenario leading to gastric cancer development is chronic gastritis in the corpus leading to impaired acid secretion in the stomach, which leads to bacterial overgrowth and increased bacterial production of carcinogenic nitrosamines from nitrates in the diet. The lack of ascorbic acid in the diet promotes the formation of *N*-nitroso mutagens in the gastric lumen.

Intestinal metaplasia is defined as the replacement of normal gastric epithelium with columnar epithelium similar to the small intestine or colon. Three types of intestinal metaplasia have been described based on morphologic criteria and mucin histochemistry. Type I intestinal metaplasia is characterized by straight crypts with well-developed goblet and absorptive cells. Goblet cells contain sialomucins and absorptive cells are nonsecretory. Type II intestinal metaplasia is characterized by less well differentiated small intestinal epithelium. Type III intestinal metaplasia is characterized by tortuous crypts with immature columnar cells and goblet cells containing sulfomucins. Several studies have shown that Type III intestinal metaplasia is most commonly associated with gastric cancer, usually of the intestinal type.

Other conditions associated with chronic gastritis have also been associated with increased risk for the development of gastrointestinal cancer. Chronic gastritis due to pernicious anemia is categorized as type A (autoimmune) and typically involves the body and fundus rather than the antrum. The increased risk attributable to pernicious anemia is considered to be small. In a recent large retrospective study of patients with pernicious anemia, the ratio of observed to expected gastric cancers was 3.2. Increased risk for gastrointestinal cancer is also found in patients with a previous partial gastrectomy with a Bilroth II anastomosis and in patients who have had a Bilroth I anastomosis or a vagotomy and pyloroplasty. The increased risk following gastric surgery occurs after a period of 10–15 years. In addition to atrophic gastritis, achlorhydria, a vagotomy, and duodenogastric reflux are factors contributing to the development of gastric cancer in this setting. Patients with congenital or acquired immunodeficiency states, including acquired immunodeficiency syndrome (AIDS), are at increased risk for the development of gastrointestinal lymphomas. Celiac sprue is a risk factor for intestinal lymphomas, which usually occur in the jejunum or may be multifocal. Inflammatory bowel disease is a risk factor for the development of adenocarcinoma and possibly lymphoma. The increased risk for cancer in the patients described above is not considered to be high enough to warrant routine endoscopic screening.

Gastric cancer can be divided into two different histologic subtypes, with differing biologic characteristics that may reflect differing etiologic factors (Table 24–2). The first type is termed "intestinal" and is characterized by gland formation, and often appears similar to colon carcinoma. The second type is termed "diffuse" and is characterized by poorly differentiated cells that cluster in sheets or nodules and is devoid of gland-like structure. The intestinal type is the predominant form found in areas with epidemic gastric cancer and is associated with atrophic gastritis and intestinal metaplasia. This type is more common in males and the elderly. The diffuse type is more common in endemic areas and is not typically associated with precursor lesions in the stomach. This type is more common in women and in younger patients.

Aneuploidy is defined as an abnormal amount of DNA per cell and can be detected by flow cytometry in fresh or formalin-fixed specimens. A number of studies have determined that aneuploidy is present in 40–70% of gastric adenocarcinomas. The presence of aneuploidy correlates with increased pathologic stage and worse survival.

A number of specific genetic abnormalities have been described in gastric adenocarcinomas, which appear similar regardless of the country of origin. Chromosomal alterations include frequent deletions of portions of chromosomes 5q, 17p, and 18q, which are the sites of tumor suppressor genes APC and MCC, p53, and DCC, respectively. Abnormalitites of these tumor suppressor genes are found in 40–60% of gastric cancers. These sites are frequently altered in other cancers, such as adenocarcinoma of the colon. In general, more advanced cancers are associated with more numerous chromosomal abnormalities. The p53 gene product is a DNA binding phosphoprotein that plays a role in proliferation, apoptosis, and DNA repair, and is the most common genetic abnormality found in cancers. Altered p53 is found more frequently in advanced gastric cancers and is associated with a worse prognosis.

Several alterations of dominantly acting oncogenes have been described in gastric adenocarcinomas. Oncogenes related to fibroblast growth factor (*hst*-1/*int*-2) and fibroblast growth factor receptors (K-*sam*) are frequently amplified or overexpressed. Amplification or overexpression of *HER2/NEU* (*erb*B-2, a receptor related to the epidermal growth factor receptor) is associated with lymph node metastases and a worse prognosis, and is an independent predictor of survival in one multivariate analysis. In contrast to colon adenocarcinomas, mutations or overexpression of the *ras* family of oncogenes occur rarely in gastric adenocarcinomas. Precursor lesions such as su-

Table 24–2. Morphologic and histopathologic classification systems for gastric adenocarcinoma.

Classification	Characteristics	Associations	Prognosis (Compared with Average Survival)
Lauren			
Intestinal	Gland-like structures	Epidemic prevalence, associated with precursor lesions, men and older patients	Better
Diffuse	Poorly differentiated, unorganized sheets of cells	Endemic prevalence, younger patients and women	Worse
Broder's			
I	Well differentiated, tubular-like arrangement of cells		Better
II	Moderately differentiated, irregular tubules		
III	Poorly differentiated, irregular sheets of cells		
IV	Anaplastic		Worse
Ming			
Expansive	Discrete tumor nodules growing by expansion	Associated with intestinal metaplasia, M:F = 2:1, 6% under age 50	Better
Infiltrating	Tumor cells individually invade surrounding tissue	M:F = 1:1, 14% under age 50	Worse
Borrmann			
I	Polypoid or fungating		Better
II	Ulcerated with elevated borders		
III	Ulcerated and infiltrating gastric wall		
IV	Diffusely infiltrating		
V	Unclassifiable		Worse

perficial gastritis or gastric dysplasia may also demonstrate genetic alterations, such as altered expression of tyrosine kinase growth factor receptor *met, ras* oncogenes, and p53. However, the relationship of specific genetic abnormalities and progressive stages of gastric carcinogenesis has not been completely defined.

Prior *H pylori* infection has been associated with primary gastric lymphomas, but not with lymphomas of other sites. *H pylori*-induced gastritis is characterized by infiltration of the mucosa with lymphocytes. This is thought to give rise to the development of low-grade gastric lymphomas that resemble mucosa-associated lymphoid tissue (MALT) rather than lymphomas associated with lymph nodes. Low-grade MALT lymphomas and high-grade B cell lymphomas may be found together in patients with gastric lymphoma, and it is thought that low-grade MALT lymphomas may be a precursor to high-grade gastric lymphomas.

Chromosomal abnormalities play an important role in the pathogenesis of lymphocytic lymphomas of the gastrointestinal tract. More than 90% of lymphocytic lymphomas display cytogenetic abnormalities, and greater numbers of these abnormalities are associated with higher grade tumors. Molecular genetics of lymphomas are characterized by translocation of DNA from one chromosome to another. Clinically important translocations appear to bring oncogene regions in proximity to immunoglobulin genes. The t(8;14) and t(8;22) translocations bring the *myc* oncogene on chromosome 8 close to immunoglobulin heavy chain or light chain loci, respectively. This results in upregulation of *myc* gene expression, which is a DNA-binding protein involved in control of proliferation. The t(14;18) trans-location juxtaposes the B cell leukemia lymphoma-2 gene (*BCL2*) and the immun-oglobulin heavy chain joining region on chromosome 14. These lead to increased *BCL2* protein expression, which is an inner mitochondrial membrane protein that contributes to tumor proliferation by blocking programmed cell death (apoptosis). Other genes that are implicated in translocations in lymphomas include *BCL1, PRAD1* (a cell-cycle regulatory protein or cyclin), and T cell receptor genes (*TCRα, TCRδ, TCRβ TCRγ).* Interestingly, low-grade MALT-type lymphomas of the stomach characteristically do not demonstrate rearrangement of the BCL2 gene. The differences in molecular alterations in gas-

trointestinal and nongastrointestinal lymphomas and the relationship of molecular changes in precursor and early stage lymphomas with late stage lymphomas have not been well characterized.

GISTs consistently express the *c-kit* gene, located on chromosome 4q11–21. The *c-kit* gene encodes a transmembrane receptor protein with an internal tyrosine kinase component. Gain-of-function mutations in exon 11 (and rarely exons 9 and 13) of the *c-kit* gene have been described in GISTs, which lead to ligand-independent tyrosine kinase activation. Studies have shown that 21–88% of predominantly malignant GISTs have *c-kit* mutations. The activated c-kit tyrosine kinase has recently been exploited as a target for chemotherapeutic inhibition, with good clinical response rates reported.

Clinical Findings

A. Symptoms and Signs

Symptoms associated with early gastrointestinal tumors are often minimal and/or nonspecific. The initial symptoms attributable to a tumor depend on the location of the tumor. Obstructing lesions of the lower esophagus and gastric cardia often cause dysphagia to solid foods. Because of this location, tumors of the lower esophagus and gastric cardia may be diagnosed at an earlier stage compared with tumors of the body or antrum. Early tumors in the body or antrum are asymptomatic or cause vague abdominal discomfort or "fullness," dyspepsia-like symptoms, nausea, or diminished appetite. Patients often will alter their diet in an attempt to ameliorate these symptoms. Symptoms of gastric outlet obstruction, early satiety, and weight loss are indicative of a large or advanced-stage tumor. Early satiety results from infiltration of the gastric wall and loss of distensibility. Gastric tumors may also cause occult gastrointestinal blood loss and the development of symptoms due to iron deficiency anemia.

Because the symptoms of early stage gastric tumors are minimal or mimic those of acid-peptic disease, the diagnosis is often delayed. Consequently, the proportion of patients diagnosed with advanced stage tumors is high. Diagnosis of operable gastric cancers requires a high index of suspicion and early referral for endoscopy or radiologic studies. If dyspeptic symptoms are accompanied by weight loss, vomiting, dysphagia, or evidence of gastrointestinal (GI) blood loss, endoscopy should be performed first before any therapeutic trials are initiated. Of particular concern are new "dyspeptic" symptoms that develop in patients over 40 years of age. Predisposing factors such as prior gastric resection, pernicious anemia, or prior gastric adenomas should also be taken into consideration and prompt early diagnostic studies.

The indications for endoscopy in patients presenting with dyspepsia and no other symptoms are evolving. Physicians may elect to treat simple dyspeptic symptoms with a course of H_2 blocker therapy and proceed to endoscopy only for persistent symptoms following a 1- to 2-month course of therapy. Many physicians will attempt to diagnose *H pylori* infection and associated ulcers prior to initiating treatment.

Tumors of the small intestine usually present with pain, obstructive symptoms, or bleeding. The pain is cramping and intermittent and results from partial lumenal obstruction. Other symptoms include nausea, vomiting, anorexia, altered bowel habits, and weight loss. Gastrointestinal bleeding is usually self-limited or occult. Patients presenting with melena or iron deficiency anemia should have a dedicated radiologic examination of the small intestine or enteroscopy if endoscopic studies of the gastroduodenum and colon do not reveal a cause. Similarly, occult fecal blood loss associated with anemia or symptoms should be evaluated in a similar fashion.

Less frequently, gastric and small intestinal tumors may present as a gastrointestinal emergency, such as massive hemorrhage, acute obstruction, intussusception, or perforation. Adenocarcinomas, lymphomas, and leiomyosarcomas may present with acute gastrointestinal hemorrhage and require management in intensive care units and blood transfusion. Diagnosis is initially attempted using endoscopic procedures. Injection or thermal endoscopic therapies that have been shown to be effective for bleeding peptic ulcers are often not successful if the bleeding is caused by a malignancy. Continued bleeding should be treated by urgent laparotomy or angiographic vessel occlusion. Leiomyosarcomas may present with acute bleeding into the peritoneal cavity with little intralumenal blood loss.

Patients with acute obstruction present with persistent nausea, vomiting, and abdominal pain. Flat and upright films of the abdomen may demonstrate dilated small intestine and air–fluid levels above the site of obstruction. Perforation should be considered if the pain is severe, constant, and associated with rebound tenderness, fever, and/or leukocytosis. The primary diagnostic and therapeutic procedure for patients presenting with acute obstruction or perforation is surgical; therefore early consultation with a surgeon is mandatory for patients presenting with these symptoms. Perforation is a sign of an advanced tumor and is associated with a worse prognosis.

Symptoms do not distinguish carcinoid from other tumors of the intestine unless the carcinoid is advanced and produces the carcinoid syndrome. The development of carcinoid syndrome depends on a large tumor mass with drainage into the caval circulation. This is found with hepatic metastases, with carcinoids develop-

ing in large teratomas of the ovaries or testes, or with large tumors that invade retroperitoneal vessels. Symptoms are thought to result from serotonin or other vasoactive substances synthesized by the tumor. The majority of patients complain of diarrhea and flushing episodes. Asthma and pellagra may occur in less than 10% of patients. Diagnosis of carcinoid syndrome is made by the demonstration of elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) levels.

Physical examination often is not helpful in patients with early gastrointestinal tumors. Guaiac tests of stool obtained on rectal examination should be performed. Pallor and cachexia often indicate an advanced stage of gastric cancer. Palpation of the abdomen occassionally reveals an epigastric mass; however this is also evident only with advanced disease. Gastrointestinal lymphomas and leiomyomas may present with a palpable mass in 20–50% of cases. Advanced gastric adenocarcinomas may be associated with physical signs of distant metastases. These include hepatomegaly, ascites (due to peritoneal involvement or secondary to portal hypertension from extensive liver metastases), left supraclavicular lymphadenopathy (Virchow's node), left anterior axillary adenopathy (Irish's node), umbilical nodules (Sister Mary Joseph's node), a rigid rectal prominance above the prostate (Blumer's shelf), and ovarian metastases (Krukenberg tumor). Rare skin abnormalities associated with gastric cancer include acanthosis nigricans, dermatomyositis, metastatic nodules, or warty keratosis and pruritus (sign of Leser-Trelat).

B. Laboratory Findings

Evidence of iron deficiency anemia should always prompt an evaluation of the gastrointestinal tract, including upper and lower GI endoscopic procedures. If these procedures are negative a small bowel barium examination should be preformed. Abnormalities of liver function tests may suggest hepatic metastases. Asymptomatic patients without anemia who are found to have a positive stool guaiac on routine screening should have a colonoscopic or barium examination of their colon only, as the finding of gastric or small intestinal malignancies under these conditions (in North American patients) is exceedingly small.

C. Endoscopy

Upper gastrointestinal endoscopy provides a sensitive and specific method for diagnosis of gastric tumors. The size and location of abnormalities should be carefully documented during endoscopy. All abnormal mucosal lesions such as ulcers, polyps, strictures, and thickened gastric folds should be biopsied. One study has shown that accurate histologic diagnosis of gastric adenocarcinoma is possible in 95% of cases when four biopsies are taken from a specific lesion. Diagnostic accuracy increases to 98% when seven biopsies are taken, and if seven or eight biopsies and cytologic brushings or aspirates are taken diagnostic accuracy approaches 100%. Biopsies should be taken from both the margin and base of ulcer-like lesions. Because visual endoscopic assessment of malignancy is inaccurate, it is recommended that cytology and at least four to seven biopsies be obtained from all gastric mucosal lesions.

Several endoscopic features of gastric ulcers are more commonly associated with malignancies; however, differentiation of benign and malignant gastric ulcers by endoscopic appearance alone is not reliable. The size of an ulcer is an important risk factor for malignancy, as up to 20% of ulcers over 3 cm in diameter have been shown to be malignant. Other endoscopic features more frequently associated with malignancy include an irregular base, an irregular ulcer margin (which can be interrupted by tumor nodules), and disruption or abruptly cut-off folds adjacent to the ulcer. All gastric ulcers (with the possible exception of superficial ulceration associated with aspirin and nonsteroidal antiinflammatory drugs) should be followed with repeat endoscopy and biopsy until healed.

Gastric adenocarcinomas have been classified according to their gross appearance. The original classification system was proposed by Borrmann in 1926 and consisted of protruding and flat or depressed types of cancers, with the protruding type considered to have a better prognosis (see Table 24–2). This classification was modified by the Japanese Research Society for Gastric Cancer in 1981. The relationship of tumor contour and prognosis has not been consistent. The most common endoscopic appearance of gastric lymphoma is the presence of large folds in the body or antrum with diffuse ulceration. This is similar to the Bormann IV appearance of advanced gastric adenocarcinoma.

The majority of gastric polyps are benign, and again there are no reliable endoscopic features to differentiate benign from malignant. Polyp size >1 cm is a risk factor for the presence of neoplasia (adenoma) or malignancy (Figure 24–1). Biopsy of small polyps (<1 cm) is sufficient for diagnosis. Larger polyps should be biopsied to determine if neoplastic; however this may miss neoplastic foci within the polyp. Before removal of large polyps by endoscopic polypectomy or surgery, the physician must consider the histology obtained on biopsy, clinical symptoms attributable to the polyp, and the patient's age and medical status, in order to determine if polyp removal warrants the risk of the procedure. Endoscopic removal of large gastric polyps may be associated with a 4% risk of postpolypectomy bleeding, which may require surgery.

Submucosal polyps are less common than epithelial polyps (see Table 24–1). Because these lesions are submucosal, large forceps biopsies and double biopsies

Size (mm)	Lesion configuration I	II	III	IV	Total
≤ 4	○2	○8			10
5–9	○2	○13 ◒2	○24	○12	53
10–19	○7	◒2	○8 ◒4	○31	52
20–29	○1	○2	◒1 ●1	○4 ◒2	11
≥ 30	○1	◒5 ●1	◒8 ●9	◒1 ●1	26
Total	13	33	55	51	152

○ Benign
◒ Early gastric cancer
● Advanced gastric cancer

Figure 24–1. The relationship of lesion size, shape, or configuration, and histology for 217 elevated lesions of the stomach diagnosed with double contrast radiography. Malignancy occurs more frequently in lesions over 1 cm in diameter. (Reproduced, with permission, from Yamada T, Ichikawa H: X-ray diagnosis of elevated lesions of the stomach. Radiology 1974;110:79.)

(biopsies within previous biopsy sites), especially in suspicious areas such as central ulcerations, should be performed. Infiltrating adenocarcinoma and lymphomas may also occur in the submucosa. Infiltrating adenocarcinoma (linitis plastica) may be difficult to recognize endoscopically. Subtle changes in gastric folds and areas with poor distensibility should be biopsied. Again, large biopsies and biopsies within biopsies may be required to make a diagnosis. If clinical and/or endoscopic findings suggest malignancy and biopsies and brushings are negative, large-particle snare biopsy or needle aspiration cytology during endoscopic ultrasound examination should be performed. Laparotomy may be required to obtain a histologic diagnosis.

Small bowel enteroscopes may be used to examine the small intestine, and have primarily been used in patients with gastrointestinal bleeding and no identifiable source on standard upper and lower GI endoscopies. "Push" enteroscopy entails the use of colonoscopes 135–160 cm in length or special 167-cm-long enteroscopes that are inserted through the mouth and into the proximal small intestine under direct visualization. Examination of 50–60 cm beyond the ligament of Treitz can be accomplished with this method. "Sonde-type" enteroscopes are more effective for examination of the distal small intestine. These contain a balloon at the tip that allows for peristalsis to propel the enteroscope into the ileum. Using "Sonde-type" enteroscopy, small intestinal lesions have been identified in one-quarter to one-third of patients examined for unexplained gastrointestinal blood loss. Small intestinal tumors have been found in 5% of patients examined by small bowel enteroscopy under these conditions. Diagnosis of small bowel tumors by small bowel enteroscopy has been reported in cases in which other imaging modalities, including enteroclysis and angiography, have been negative. The "Sonde" technique is limited by the length of time required for passage of the enteroscope (mean 4–8 hours) and lack of tip deflection and biopsy capabilities. Intraoperative endoscopy of the small bowel can also be performed. This involves passage of a colonoscope through the mouth or anus by the endoscopist. The surgeon then manually telescopes loops of bowel over the endoscope.

Routine surveillance endoscopy for gastric cancer is performed in Japan due to the high prevalence of cancer in that country. In the United States routine surveillance endoscopy for gastric cancer in asymptomatic patients with *H pylori* gastritis, pernicious anemia, or who have had a previous gastrectomy is generally not recommended.

D. Imaging

Computed tomography (CT) scans of the chest and abdomen are the primary imaging modalities for preoperative staging of stomach and small intestine tumors. In stomachs that are well distended with contrast, wall thickness of >2 cm indicates transmural extension of the tumor (Figure 24–2). Evidence of direct invasion of perigastric fat, diaphragm, pancreas, transverse colon, and left lobe of the liver should be sought. Metastases to the liver, lung, and other organs can also be documented. For gastric adenocarcinoma overall accuracy of preoperative CT scans ranges from 61 to 72%. CT scans are particularly unreliable in assessing regional lymph nodes and invasion of adjacent organs, resulting

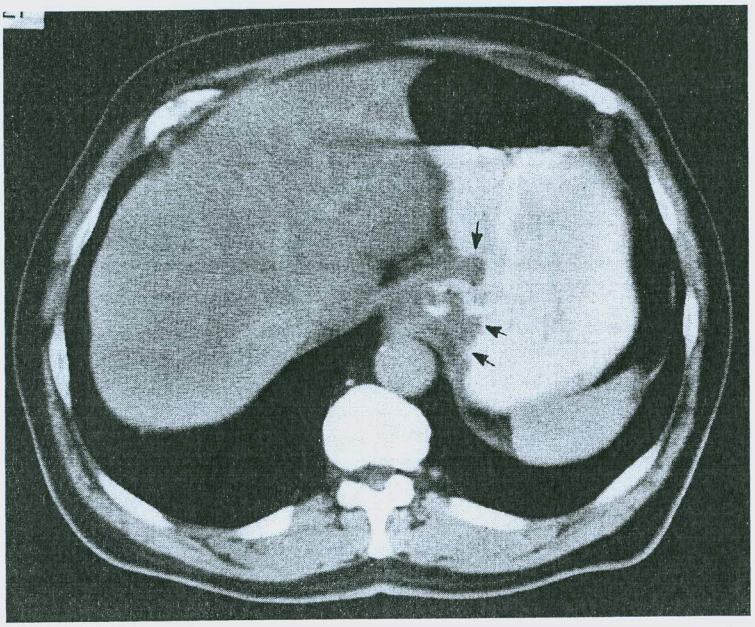

Figure 24–2. CT examination of the abdomen. Arrows denote tumor mass, a gastric adenocarcinoma of the cardia. (Courtesy of Dr. Howard Ansel.)

in understaging of the disease. CT scans may also overstage gastric adenocarcinoma, resulting in labeling the cancer as unresectable when in fact the tumor may be resectable. In one study comparing preoperative CT scanning with surgical staging it was found that 31% of patients were understaged and 16% were overstaged by CT. Careful review of preoperative CT scans by the gastroenterologist, surgeon, and radiologist is necessary before making a decision regarding resectability.

Endoscopic ultrasound is able to increase the accuracy of preoperative staging by determining the depth of invasion and possibly the involvement of regional lymph nodes. Several studies have compared endoscopic ultrasound, CT scans, and subsequent operative staging. Endoscopic ultrasound demonstrated 83–88% accuracy for determining depth of invasion compared with 35% accuracy for CT. For determining nodal involvement, endoscopic ultrasound is 66–72% accurate compared with 45% accuracy for CT.

Radiologic examination of the stomach can identify advanced gastric cancers; however it is less accurate than endoscopy for identification of early gastric cancer. All ulcers identified by x-ray examination should be referred for endoscopic biopsy. Radiologic criteria that suggest a benign ulcer include radiating folds and a normal-appearing mucosal surface around the crater. Linitus plastica is suggested by radiologic studies that demonstrate a nondistensible stomach.

Radiologic examination of the small bowel remains the most widely used method for diagnosis of small intestinal tumors (Figure 24–3). It is essential to communicate with the radiologist that a small bowel tumor is suspected, so that a dedicated small bowel examination can be performed. The "small bowel follow-though" that accompanies an upper GI x-ray is often inadequate for diagnosis of small bowel tumors. Enteroclysis, performed following placement of a nasoduodenal tube, is the most sensitive test for diagnosis of intestinal tumors, particularly if they occur in the jejunum. If an ileal lesion is suspected, a small bowel follow-through with air insufflated in the colon should be performed, which provides a clear air-contrast examination of the ileum. Patients actively bleeding from a suspected small bowel source should undergo a nuclear medicine tagged red blood cell (RBC) examination followed by angiography if the bleeding is continuous. Patients with gastrointestinal blood loss who are not actively bleeding and in whom a small bowel lesion is suspected should undergo a nuclear medicine Meckel's scan prior to barium studies. In addition to identification of Meckel's diverticula, this scan will occassionally identify leiomyomas or leiomyosarcomas, and can be followed by angiography or laparotomy to confirm the diagnosis.

A new and promising approach to imaging the small intestine to diagnose tumors and other sources of occult bleeding is a small capsule containing a light source and video chip camera, which can be swallowed. As the capsule passes through the small intestine, it transmits video images and information concerning its location to a recording device worn by the patient. These images

A B

Figure 24–3. **A:** Primary jejunal adenocarcinoma ***(arrows)*** diagnosed with a small bowel follow-through barium examination. Bowel proximal to the tumor is dilated. **B:** Metastatic adenocarcinoma of the small bowel ***(arrows)*** diagnosed with a small bowel follow-through examination. (Courtesy of Dr. Howard Ansel.)

can then be reviewed, providing near-complete imaging of the small intestine.

Differential Diagnosis

Ulcerative and polypoid lesions of the stomach and intestine must be differentiated into benign and malignant. All ulcers found in the stomach require endoscopic biopsies and brushings at the time of initial diagnosis. A history of aspirin or nonsteroidal antiinflammatory drug use should be sought. Ulcers should also be followed with repeat endoscopy after a course of therapy in order to determine if they have healed, and repeat biopsies should be taken if nonhealing is demonstrated. Occasionally, malignant ulcers may appear to heal or partially heal following acid supression therapy and therefore repeated biopsies and brushings are important.

Most polyps found in the stomach represent hyperplastic polyps and usually occur in response to inflammation (see Table 24–1). Adenomatous polyps are the second most frequent type of gastric polyp and are considered precancerous. Adenomas should be removed by endoscopic polypectomy or surgical removal. The risk of malignancy increases in polypoid lesions greater than 1 cm in diameter, and surgical resection should be considered if a definitive diagnosis cannot be made by endoscopic biopsy. Less frequently, benign gastric polyps may represent carcinoid, leiomyoma, lipoma, and pancreatic rests. The latter represent ectopic pancreatic tissue, usually located in the submucosa of the antrum. Pancreatic rests may have a central umbilication or ulceration, and may present with bleeding, obstruction, or rarely clinical pancreatitis.

Gastric polyps frequently occur in patients with familial polyposis coli. Typically, hyperplastic polyps are found in the fundus and adenomatous polyps in the distal stomach and duodenum. Duodenal and periampullary adenocarcinoma can occur in 1 of 21 patients with familial polyposis coli over a lifetime. Screening endoscopy with careful attention to the duodenal ampulla and removal of all polyps has been recommended for these patients every 4 years. Peutz-Jeghers syndrome is an autosomal dominant condition characterized by intestinal polyps and pigmentation of the lips, buccal mucosa, hands, feet, or eyelids. Gastric hamartomas occur in 25% of patients with Peutz-Jeghers syndrome. Large folds (>1 cm in height) in the stomach that may resemble infiltrative malignancy may occur with hypertrophic gastritis and Menetrier's disease. The latter is a very rare condition characterized by mucosal hyperplasia and cystic dilation of gastric glands. Gastric folds in the fundus, body, and occasionally antrum appear enlarged, erythematous, and convoluted. Patients present with abdominal pain and hypoproteinemia.

Metastatic cancers may occur in the stomach and should be considered in any patient with gastrointesti-

nal symptoms and history of a prior nongastric malignancy. The most common metastatic cancers to the stomach or small intestine include lung, breast, and melanoma (Figure 24–3B). These may appear as polypoid lesions with or without erosions or ulceration. Metastatic melanoma characteristically may appear as target or "bull's eye" lesions on a barium x-ray of the stomach, and at endoscopy often appear as small, discrete brown tumor nodules. Larger melanomas may appear as plaques with peripheral pigmentation, submucosal tumors with central ulceration, or large amelanotic masses. Metastatic breast carcinoma may present with a linitus plastica-type appearance. Other cancers that may metastasize to the stomach include cancer of the ovary, testes, liver, colon, and parotid gland.

Kaposi's sarcoma is a common tumor in patients with AIDS, and may be found in the gastrointestinal tract in up to 50% of patients with AIDS-related Kaposi's sarcoma. The endoscopic appearance may consist of erythematous nodules ranging in size from 1 to >5 mm, with or without central erosions. The appearance may also resemble gastric lymphoma with polypoid-type lesions.

Pseudotumors are lesions that simulate common tumors in the intestine. These include inflammatory pseudotumors or fibroid polyps (accumulation of fibroblasts), invasion of the gut wall by nematodes (helminthic pseudotumor), intestinal endometrioma, and amyloidosis.

Staging

A. Gastric Adenocarcinoma

Initial staging of gastric adenocarcinoma includes determination of operative resectibility. This requires a complete history and physical examination to evaluate for concomitant medical problems and ability to undergo abdominal surgery. Local staging of the actual tumor includes determination of the size and location of the tumor by endoscopy. Biopsies should be taken of apparently normal mucosa distal and proximal to the lesion to rule out infiltrative or submucosal spread. CT scans of the abdomen and chest are required to determine extent of disease into adjacent organs, possible lymph node involvement, and distant metastases. Careful questioning for new skeletal symptoms may direct x-ray or bone scan evaluations for osseous metastases. Patients with gastric tumors are generally considered operative candidates if they have no serious concurrent medical problems and when there is no evidence of distant metastases to liver, lung, or other organs.

The most commonly used staging system in the United States is the American Joint Committee on Cancer Staging System (Table 24–3). This system incorporates depth of invasion (T), location of nodal metastases (N), and distant metastases (M). This staging system is similar to the Union Internationale Contre le Cancer (UICC) TNM system used in Europe. Japanese surgeons have developed a rigorous staging system that requires extensive nodal dissection at the time of surgery. This staging system also incorporates gross (Bormann's classification) and microscopic (Lau-

Table 24–3. American Joint Committee on Cancer staging of gastric cancer.

Stage	Primary Tumor	Classification		5-Year Survival Rate
0	Tis	N0	M0	>90%
IA	T1	N0	M0	70–80%
IB	T1	N1	M0	55–70%
	T2	N0	M0	
II	T1	N2	M0	40–50%
	T2	N1	M0	
	T3	N0	M0	
IIIA	T2	N2	M0	10–20%
	T3	N1	M0	
	T4	N0	M0	
IIIB	T3	N2	M0	
	T4	N1	M0	
IV	T4	N2	M0	<1%
	Any T	Any N	M1	

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
Regional lymph nodes (N)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in perigastric lymph nodes within 3 cm of edge of primary tumor
N2	Metastasis in perigastric lymph nodes more than 3 cm from edge of primary tumor, or in lymph nodes along left gastric, common hepatic splenic or celiac arteries
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

ren's classification) pathologic characteristics of the cancers. As a consequence, comparison of cancers by stage from Japan and other countries is not often accurate.

"Early" gastric cancers are characterized by their location in the mucosa and submucosa (T1), and may or may not have nodal metastases. By definition, early gastric cancers include stage IA (T1N0), stage IB (T1N1), and stage II (T1N2) tumors. Not surprisingly, early gastric cancers are associated with excellent survival from surgical resection. Early gastric cancers account for only 15% of the cases in the United States. In contrast they comprise 40% or more of cancers reported in Japan, most likely due to extensive endoscopic surveillance programs. In Western countries 70–80% of resected gastric cancer specimens have advanced disease with metastases in the regional lymph nodes.

B. Lymphoma

Primary gastrointestinal lymphoma staging is adapted from the Ann Arbor staging system for lymphoma (Table 24–4). This staging system does not take into account several other criteria that have been shown to be associated with an adverse prognosis. These include size of tumor at presentation >7 cm, B-type symptoms (fever, sweats, weight loss), elevated serum lactate dehydrogenase and β_2-microglobulin, advanced depth of invasion and level of lymph node involvement, abdominal perforation, increased number of sites, nonresectability, advanced age, and the presence of comorbid disease. In addition to a physical examination, staging can be accomplished by intestinal barium studies, CT scans of the chest, abdomen, and pelvis, indirect laryngoscopy, and bilateral bone marrow biopsy and aspirates. Gallium scanning, bipedal lymphangiography, and a laparoscopic liver biopsy may also be used to complete the work-up. One-third of patients are diagnosed with stage IE lymphoma, one-third to one-half are diagnosed with stage IIE, and less than one-quarter are diagnosed with stage IV disease.

Table 24–4. Modified Ann Arbor staging system for primary gastrointestinal lymphoma.

Stage	Extent of Involvement
IE	Limited to one area of the GI tract with no other site
IIE	Localized involvement of an extranodal GI site and its lymph node chain
II_1E	Limited to the GI site and immediately draining lymph nodes
II_2E	A primary GI extranodal site and involvement of immediate and noncontinuous subdiaphragmatic lymph node groups
IIIE	Involvement of lymph nodes on both sides of the diaphragm and localized involvement of a dominant extranodal GI site
IV	Diffuse or disseminated involvement

Treatment & Prognosis

The primary mode of treatment of most gastric and small intestinal tumors is surgical. Prognosis is directly related to the type and stage of the tumor and the completeness of the surgical resection.

A. Gastric Adenocarcinoma

The overall 5-year survival for gastric adenocarcinoma has changed little in the last several decades in the United States and currently remains at 10–15%. Early gastric cancer is curable with surgical resection, however this type comprises only 5–16% of patients undergoing resection for gastric cancer. In the United States, approximately 60% of patients with gastric cancer will have nonresectable disease at the time of diagnosis. Of the remaining 40% who have a "curative" resection (termed R0 resection), only 25–35% will survive 5 years (Figure 24–4).

Gastric adenocarcinomas are optimally resected using wide margins and with extensive lymph node dissections. Total gastrectomies are not routinely performed due to the increased morbidity associated with this procedure, but may be required if the tumor is extensive or multifocal. The Japanese Research Society for Gastric Cancer groups gastric lymph nodes (D1–D4) according to their proximity to the stomach. Curative resection requires resection of tumor-free lymph nodes in at least one group distant to involved lymph nodes and also often includes removal of the omentum and spleen. Extended or radical lymph node dissections have long been performed in Japan and may contribute to the extended survival found in Japanese patients with early stage cancer. The use of extended lymphadenectomies in Western countries is controversial, and several studies have not demonstrated a survival advantage with this procedure. Recent European studies have shown that extended D2 level lymph node resections result in higher morbidity and mortality than D1 level lymph node resections, with no survival advantage. Extended D2 level lymphadenectomies may benefit patients with serosal invasion or limited regional node disease; however, it most likely is not beneficial for patients with D3 node involvement, linitus plastica, and extensive invasion of adjacent organs.

Surgical resection should be considered even if CT scans suggest locally advanced disease. Occasionally a curative resection can be performed by en bloc resection of the tumor and adjacent involved organs. If the lesion is extensive and complete removal does not ap-

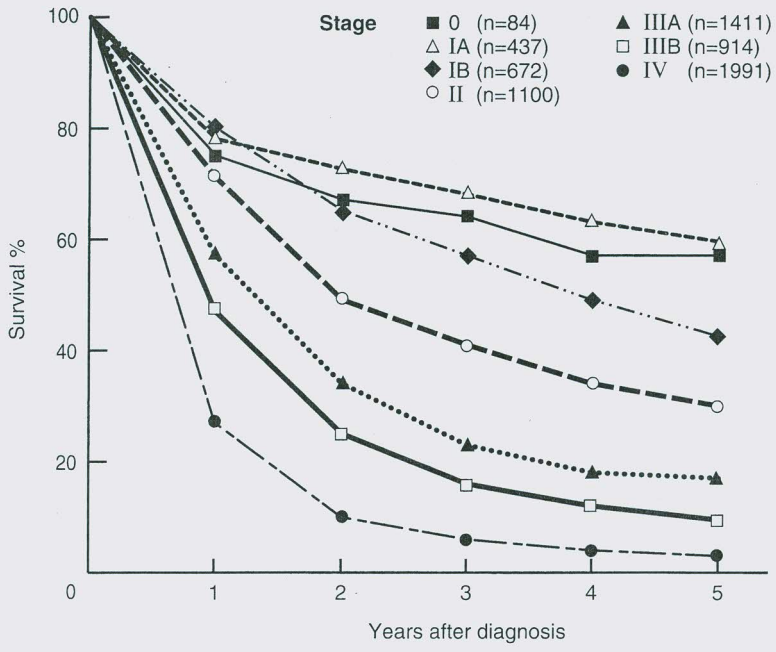

Figure 24–4. Survival by TNM classification and staging of 6609 patients with gastric adenocarcinoma. Stage IA versus IB, $P < .01$; stage II versus IB, IIIA, or IIIB, $P < .01$. (Reproduced, with permission, from Thompson GB, van Heerden JA, Sarr MG: Adenocarcinoma of the stomach: are we making progress? Lancet 1993;342:713. © by The Lancet Ltd., 1993.)

pear possible, a palliative resection can be planned. Survival and symptoms are improved if a palliative resection is performed instead of a simpler bypass procedure. Bypassing obstructing lesions with a gastrojejunal anastomosis may be the only surgical option for maintenance of fluid intake in some cases of advanced gastric cancer. Laparoscopic staging of patients with apparent locoregional carcinoma should also be considered.

Treatment guidelines for patients with gastric cancer have been published by the National Comprehensive Cancer Network (NCCN). Current recommendations indicate that patients with negative surgical resection margins and no evidence of metastases (R0 resection) be observed and receive no further therapy. Results of multicenter adjuvant therapy studies are pending for this type of patient. Patients with positive surgical resection margins (R1 resection) should be offered radiotherapy (45–50 Gy) with concurrent 5-fluorouracil (5-FU) chemotherapy. Patients with gross residual disease (R2 resection) and no metastases after surgery can be offered 5-FU chemotherapy with or without radiation therapy, cisplatin-based chemotherapy, or enrollment in a clinical trial. For inoperable patients with locoregional carcinoma, radiation therapy with concurrent 5-FU treatment, "salvage" chemotherapy with 5-FU or cisplatin-based therapy, or participation in a clinical trial can be recommended. Patients with a poor perfomance status (Karnofsky score ≤ 60 or ECOG score ≥ 2) should be offerred supportive care only. Following completion of chemotherapy the patients should be restaged, and if there is evidence of residual or metastatic disease then salvage therapy can be considered.

Chemotherapies in the adjuvant, primary treatment, or salvage setting are based on chemotherapeutic agents that have demonstrable activity in gastric carcinomas. A positive tumor response is defined as a 50% or greater reduction in the size of a measurable tumor. Single chemotherapeutic agents with response rates of 20–25% include 5-FU, mitomycin C, doxorubicin, nitrosoureas, and cisplatin. Combination chemotherapy with 5-FU, doxorubicin (Adriamycin), and mitomycin C (FAM) or etoposide, Adriamycin, and cisplatin (EAP) has a response rate of 22–50%. Several combinations have been described that demonstrate response rates of up to 50% in a limited number of trials. These include 5-FU, Adriamycin, and cisplatin (FAP); etoposide, leucovorin, and 5-FU (ELF); and 5-FU, Adriamycin, and methotrexate (FAMTx). Significant toxicities may occur with these regimes.

Palliation of obstructive or bleeding complications due to disseminated or recurrent gastric cancer represents a difficult management problem. For obstruction of the distal esophagus, endoscopic laser therapy or prosthetic wire mesh stents have been used successfully, or percutaneous endoscopic gastrostomy (PEG) tubes can be placed. For obstruction of the distal stomach a simple gastrojejunostomy or partial gastrectomy can be performed. Palliative resection may provide superior re-

sults compared with palliative bypass, however, at the expense of increased morbidity. Palliation of obstructing cancer at the gastric outlet may also be managed by wire mesh stents placed by endoscopy. Laser or thermal cautery therapy may be used for persistently bleeding lesions. Occasionally an obstructing tumor may respond to localized radiation therapy. However, the dose of radiation is often limited by the low tolerance of surrounding tissues.

B. Lymphoma

Definite data regarding the best treatment strategies for each stage of gastrointestinal lymphoma are lacking, and recommendations for therapy are made on the basis of the experience of a small, retrospective series of patients that used varying staging criteria. Patients with apparent stage IE or IIE disease should have surgical excision of the tumor and lymph nodes. Stage IE patients do well with surgical therapy alone, with long-term survival rates of 62–86%. The addition of adjuvant radiation therapy in this setting has not been shown to be beneficial; however most recommend postoperative radiation for extensive stage IE lesions. Patients with stage IIE lesions are often treated with adjuvant combination chemotherapy. For patients with significant residual disease after initial surgery, adjuvant radiation therapy is often used in addition to chemotherapy. Stage II_1E patients demonstrate survivals similar to stage IE, whereas stage II_2E patients usually develop progressive lymphoma within 3 years of diagnosis. Patients with stage III or IV disease should undergo radiation and/or combination chemotherapy as a primary treatment modality, with or without surgical debulking. Evidence exists to indicate that surgical debulking of stage III or stage IV disease may enhance survival and prevent the infrequent complications such as perforation or bleeding that may occur during chemotherapy. Very few 5-year survivals occur with stage III or IV disease.

C. Carcinoid

Carcinoid tumors are characterized by a slow rate of invasion and metastases. Carcinoid localized to the intestine will be cured by surgical resection in over 90% of patients. Patients with carcinoid tumors with nodal metastases at the time of surgery will have an 80% recurrence-free rate at 5 years; however after 25 years only 23% of patients will be recurrence free. Patients with unresectable abdominal tumors and patients with unresectable hepatic metastases will have a 50% and 30% survival rate at 5 years, respectively (Figure 24–5). Current therapies for treating hepatic metastases may extend these survivals and include a multispecialty approach using surgical debulking, cryoablation, hepatic artery embolization, octreotide, and possibly combination chemotherapy. For example, promising results have been obtained by treatment of unresectable hepatic carcinoid by hepatic artery occlusion with or without adjuvant chemotherapy. Patients with advanced carcinoid and the carcinoid syndrome can be palliated by treatment with octreotide, a somatostatin analogue. Chemotherapy is generally ineffective and is often not recommended except on an experimental basis. Active agents include 5-FU, doxorubicin, dacarbazine, cyclophosphamide, or streptozotocin. The response rate to these drugs is poor (approximately 20%) and the median duration of tumor regression has been reported to be 4 months.

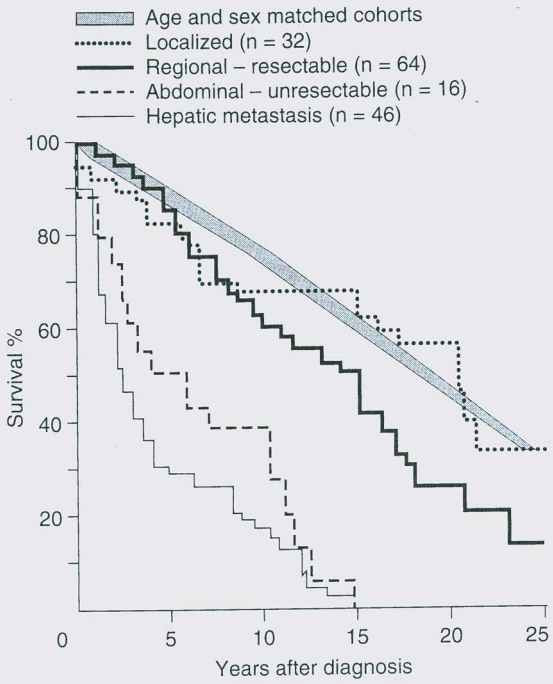

Figure 24–5. Carcinoid tumors of the small bowel. Survival is according to the stage at initial surgical diagnosis. (Reproduced, with permission, from Moertel CG: An odyssey in the land of small tumors. J Clin Oncol 1987;5:1503.)

D. Gastrointestinal Stromal Tumors (Leiomyoma, Leiomyosarcoma)

Preoperative staging is necessary to identify disseminated disease. Approximately 67% of patients with leiomyosarcoma will have extragastric extension at laparotomy, and surgical resection with curative intent is successful in up to one-half of patients. Overall, the 5-year survival for leiomyosarcoma is 25–30%. Little

efficacy has been reported for traditional radiation, chemotherapy, or both in the treatment of gastrointestinal stromal tumors. Early experience with the tyrosine kinase inhibitor, STI-571 (Gleevec, Novartis Pharmaceuticals) has been encouraging. This is a nontoxic chemotherapeutic agent that targets the *c-kit* receptor tyrosine kinase protein. This agent was recently approved by the FDA and is currently the treatment of choice for all patients with malignant GIST who have not had curative surgical therapy.

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