TUMORS OF THE STOMACH AND SMALL BOWEL

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Gastric Adenocarcinoma

The incidence of gastric carcinoma exhibits significant geographic variability. The disease is most common in Japan and China, and high rates of occurrence have also been reported in Central and South America, eastern Europe, and parts of the Middle East. In most of the more developed nations, however, gastric carcinoma is relatively uncommon. The overall incidence of this condition has decreased in the past few decades, but gastric carcinoma remains the second leading cause of cancer death worldwide. The reported reductions in gastric cancer mortality appear to be linked to better refrigeration and a concomitant decrease in the intake of salted, pickled, smoked, and chemically preserved foods. An inverse association with the consumption of fresh fruits and vegetables has also been noted.

Gastric cancer occurs 1.5 to 2.5 times more frequently in males than in females. It is rarely diagnosed before the age of 40, and its incidence peaks in the seventh decade of life. African Americans, Hispanic Americans, and Native Americans are two times more likely to have gastric cancer than are white Americans.

In the United States in particular, the incidence of stomach cancer has fallen substantially over the past 70 years. Whereas this disease was once a leading cause of cancer-related death in the United States, it now ranks 13th among major causes. Unfortunately, the decline in incidence has not translated into an improvement in the 5-year survival rate. Across all races, the 5-year relative survival was 27% for the 18,365 gastric cancer patients from Commission on Cancer-approved hospitals, 31% of tumors were found to be in the proximal stomach, compared with only 26% in the distal third. In the United States, carcinoma of the cardia occurs primarily in whites, with a male-to-female ratio of approximately 2:1. Cancer of the cardia appears to be distinct from adenocarcinoma of the distal esophagus, which frequently arises in the setting of Barrett esophagus. Associations have also been reported between cancer of the gastric cardia and infection with Helicobacter pylori or Epstein-Barr virus.

CLASSIFICATION

Adenocarcinoma of the stomach may be divided into two histologic subtypes, intestinal and diffuse. Each subtype has unique pathologic, epidemiologic, etiologic, and prognostic features. The intestinal (or glandular) subtype usually arises in the distal stomach (often after a long precancerous phase), is more common in elderly patients, and has been closely associated with atrophic gastritis and diets high in nitrates and nitroso compounds. The characteristic histologic finding is cohesive neoplastic cells that form glandlike tubular structures. The diffuse subtype occurs more frequently in younger patients and has no identifiable precursor lesion. It may develop in any part of the stomach but shows a predilection for the cardia. Cell cohesion is absent; thus, individual cancer cells infiltrate and thicken the stomach wall without forming a discrete ulcer or mass.

In general, the prognosis for the diffuse subtype is worse than that for the intestinal subtype. Whereas intestinal lesions are seen more frequently in regions with a high incidence of gastric cancer, the incidence of diffuse lesions is constant among various populations throughout the world. Accordingly, the overall decline in gastric cancer over the past century has been attributed to a decline in intestinal lesions and to a decline in the incidence of H. pylori infection (see below).

RISK FACTORS

Historical studies of specimens obtained during operation or at autopsy suggest that gastric carcinoma, especially of the intestinal subtype, frequently develops in the presence of chronic atrophic gastritis and associated intestinal metaplasia. It has generally been assumed that adenocarcinoma of the distal stomach progresses from chronic gastritis to metaplasia through the teratogenic influence of environmental factors. The most commonly studied environmental factors are the nitrates and nitroso compounds present in high levels in salted, smoked, or pickled foods consumed in areas where gastric cancer is endemic. To date, however, no prospective studies have conclusively demonstrated that modern refrigeration practices and the subsequent decline in the salting, smoking, and pickling of food have been responsible for the relative decline in intestinal gastric cancer.

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cancer. Furthermore, the intestinal subtype may arise in the absence of metaplasia. Finally, the emergence of chronic infection with *H. pylori* as the dominant risk factor for gastric adenocarcinoma has challenged the paradigm of the atrophic gastritis–intestinal metaplasia–gastric cancer sequence.

Epidemiologic studies across various populations worldwide have consistently demonstrated a strong association between *H. pylori* infection and gastric cancer. Prospective serologic studies have confirmed that persons with evidence of such infection are three to six times more likely to have gastric cancer than persons who are seronegative. Still, only a very small fraction of infected persons develop gastric cancer. It has been estimated that more than half of the world’s inhabitants may be infected with *H. pylori*—a number that dwarfs the incidence of gastric cancer. What is clear is that *H. pylori* infection of the gastric mucosa leads to a state of chronic active inflammation that lasts for decades. This inflammatory process appears to be modulated by multiple forces, including genetic and environmental factors. Inherited traits may confer susceptibility or resistance to carcinogenesis. Indeed, first-degree relatives of gastric cancer patients have a two to three times higher relative risk of contracting the disease. Gastric irritants may act as promoters, and antioxidants may have a protective effect (which may be part of the reason for the reduced risk of gastric cancer associated with diets rich in fruits and vegetables).

Unlike intestinal cancers, diffuse cancers appear not to be associated with *H. pylori* infection. Diffuse adenocarcinoma of the stomach is more common in young patients and has no known precursor lesion. The incidence of genetically associated diffuse cancers is estimated to be in the range of 5 to 10%. Familial cases of diffuse gastric cancer occur at an average age of 38 years and are inherited in an autosomal dominant fashion with 70% penetrance. Patients with blood group A have a 16 to 20% increased risk of gastric cancer.

**CLINICAL EVALUATION**

In high-risk areas (e.g., Japan), mass screening programs have been successful in identifying early gastric cancer (EGC), which is generally amenable to surgical cure. In fact, in some Japanese studies, as many as 40% of newly diagnosed patients had EGC. Screening is not used in Western countries because the incidence of gastric cancer is low enough that screening is not cost-effective. Unfortunately, in Western countries, the disease is almost always diagnosed relatively late, when it is locally advanced or metastatic. When it is superficial, gastric cancer typically produces no symptoms. As it progresses, however, a constellation of vague, nonspecific symptoms may develop, including anorexia, fatigue, weight loss, and epigastric discomfort. Dysphagia, early satiety, vomiting, and hematemesis are also seen, albeit rarely; when present, they often indicate advanced disease. Indeed, EGC has no characteristic physical findings, and many patients are not diagnosed until they present with jaundice, ascites, or a palpable mass, all of which signal incurable disease. Although rare, certain physical examination findings are indicative of metastases, including Virchow node (left supraventricular lymph node), Sister Mary Joseph nodule (periumbilical metastasis), Irish node (axillary lymph node), and Blumer shelf (metastases palpable on a rectal examination in the rectouterine or rectovesical space).

**INVESTIGATIVE STUDIES**

Until comparatively recently, an upper gastrointestinal (GI) series was often the first diagnostic test ordered to evaluate symptoms related to the upper GI tract. However, even with double-contrast techniques, which allow improved visualization of mucosal detail, false negative rates as high as 25% were reported, especially with small lesions (5 to 10 mm). Accordingly, in most large series, fiberoptic endoscopy with biopsy has replaced contrast radiography as the primary diagnostic technique. Upper GI endoscopy with biopsy has been reported to have a diagnostic accuracy of 95%. However, false negatives have been reported, especially in the context of inadequate biopsies. Thus, it is recommended that at least four biopsies be taken from the region of any atypical findings.

**STAGING**

Two major classification systems are available for staging gastric cancer. The first is the one used in Japan, where gastric cancer is staged according to the general rules for gastric study in surgery and pathology published by the Japanese Research Society for Gastric Cancer (JRGSC). This elaborate system focuses on the anatomic involvement of specifically numbered lymph node stations. The second system is the one generally used in Western countries—namely, the familiar tumor-node-metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). The AJCC/UICC staging system is based on a gastric cancer database and classifies lesions according to the depth to which the primary tumor penetrates the gastric wall. The extent of lymph node involvement, and the presence or absence of distant metastases.

The primary goal in the evaluation of gastric cancer patients is to stratify them into two clinical stage groups: those with locoregional disease (AJCC stages I to III) and those with systemic disease (AJCC stage IV). The National Comprehensive Cancer Network (NCCN) has developed consensus guidelines for the clinical evaluation and staging of patients with possible gastric cancer. These guidelines are accessible to any practitioner via the Internet at http://www.nccn.org/ and are updated annually. Multidisciplinary evaluation is recommended for all patients. A careful history is obtained and a thorough physical examination is performed, with special attention paid to performance status and to comorbid conditions that might preclude operative intervention. Initial laboratory studies include a complete blood cell count with a platelet count; determination of serum electrolyte, blood urea nitrogen, creatinine, and glucose concentrations; and a liver function panel. Chest radiography is performed, along with computed tomography (CT) of the abdomen and pelvis.

Although CT is invaluable for detecting ascites, bulky adenopathy, and significant visceral metastases, its overall accuracy in staging tumors is modest: only 70% for advanced lesions and 44% for early lesions. CT assesses lymph node involvement primarily on the basis of node size. Thus, its
sensitivity for N1 and N2 disease is low, ranging from 24 to 43%; however, its specificity is high, approaching 100%. Technical advances, such as spiral (helical) CT with intravenous contrast plus appropriate gastric distention with 600 to 800 mL of water (a negative contrast agent), have allowed modest improvements in overall staging with CT [see Figure 3]. Although improving, CT is still limited in its ability to evaluate peritoneal disease and liver metastases smaller than 5 mm.31

Given the limitations of CT, in the absence of obvious metastatic disease, locoregional staging with endoscopic ultrasonography (EUS) is vital for accurately assessing tumor penetration through the gastric wall (T stage) and ascertaining whether regional nodes (N stage) or even mediastinal or para-aortic lymph nodes may be involved [see Figure 4]. EUS is unique among imaging modalities in its ability to image the gastric wall as a five-layer structure, with each layer correlating with a histologic layer.32 The overall accuracy of EUS in determining the extent of infiltration ranges from 67 to 92%.33 EUS features that suggest lymph node metastasis include a rounded shape, hypoechoic patterns, and a size larger than 1 cm. In one study comparing preoperative findings from EUS for 29 cardia tumors with pathologic findings at operation, the overall accuracy of EUS was 72.4% (21 of 29).34 One hundred percent of node-negative tumors were correctly identified as node negative (5 of 5), and 66.7% of node-positive tumors (16 of 24) were correctly identified as N1. EUS also allows identification and aspiration of small-volume ascites. If cytologic study of the ascitic fluid confirms the presence of malignant cells, the patient is considered to have metastatic disease and therefore is not eligible for curative intent surgery. For all of these reasons, EUS is now widely accepted as superior to conventional CT in the regional staging of gastric cancer.9

The ultimate goal of any staging evaluation is to ensure that patients with metastatic disease are not treated with nontherapeutic laparotomy or other local therapies (e.g., radiation therapy), which are generally ineffective against advanced disease. Even small-volume metastatic disease identified on the surface of the liver or the peritoneum at laparotomy is associated with poor survival: in one study, patients with such disease had a life expectancy of only 6 to 9 months.35 In these situations, there is little to be gained from attempts at palliative resection.

Staging laparoscopy has proved to be highly relevant to the evaluation of patients with gastric cancer. In a study from the Memorial Sloan Kettering Cancer Center (MSKCC), the investigators performed laparoscopic exploration on 110 of 111 patients with newly diagnosed gastric cancer.36 Of these 110 patients, 94% were accurately staged, with a sensitivity of 84% and a specificity of 100%, and 37% were found to have subclinical metastatic disease. Hospital stay was substantially shorter in the 24 patients who underwent diagnostic laparoscopy with biopsy only (average 1.4 days) than in comparable patients who underwent exploratory laparotomy without resection (average 6.5 days). Finally, at the time the data were reported, none of the patients who underwent laparoscopy had required palliative surgery. Subsequent single-institution series confirmed the utility of staging laparoscopy, reporting accuracy rates ranging from 95 to 97% and occult M1 disease rates approaching 30%.37,38 Taken as a whole, the data are compelling and have led the NCCN to encourage laparoscopic staging strongly, either before or at the time of the planned resection.39

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<th>Table 1 American Joint Committee on Cancer TNM Clinical Classification of Gastric Carcinoma, 7th Edition28</th>
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<td>Primary tumor (T)</td>
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<td>T1 Tumor invades lamina propria, muscularis mucosae, or submucosa</td>
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<td>T1b: Tumor invades submucosa</td>
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<td>T2 Tumor invades muscularis propria</td>
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<td>T3 Tumor penetrates suberosal connective tissue without invasion of visceral peritoneum or adjacent structures</td>
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<td>T4a Tumor invades serosa (visceral peritoneum)</td>
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<td>T4b Tumor invades adjacent structures</td>
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<td>Regional lymph nodes (N)</td>
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<td>N0 No regional lymph node metastasis</td>
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<td>N1 Metastasis in 1–2 regional lymph nodes</td>
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<td>N2 Metastasis in 3–6 regional lymph nodes</td>
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<td>N3 Metastasis in 7 or more regional lymph nodes</td>
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<td>N3a: Metastasis in 7–15 regional lymph nodes</td>
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<td>N3b: Metastasis in 16 or more regional lymph nodes</td>
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<td>Distant metastasis (M)</td>
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<td>M1 Distant metastasis</td>
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<th>Table 2 American Joint Committee on Cancer Staging of Gastric Carcinoma, 7th Edition28</th>
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**Figure 1** American Joint Committee on Cancer staging T1, T2, T3 diagram. T1a is defined as tumor that invades the lamina propria, whereas T1b is defined as tumor that invades the submucosa. T2 is defined as tumor that invades muscularis propria, whereas T3 is defined as tumor that extends through muscularis propria into subserosal tissue.

**Management**

The trends for treating gastric cancer have shifted over the years from surgery alone to multimodality therapy including surgery and a combination of chemotherapy or chemoradiation therapy. The NCCN guidelines recommend surgery alone or endoscopic mucosal resection (EMR) for Tis or T1a tumors, surgery alone for T1b tumors, and the option of surgery or neoadjuvant chemotherapy or neoadjuvant chemoradiation therapy for T2 tumors and higher. The following sections discuss the data supporting each of these options as well as adjuvant therapy. It is important to remember the value of a multidisciplinary team in evaluating these patients because there are a variety of treatment options depending on specific patient and medical center characteristics. As is discussed in the following section about implementation of the consensus guidelines, there has been a dramatic shift in the United States from surgery alone to perioperative chemotherapy and chemoradiation therapy.

**Surgical Therapy**

Surgical resection remains the only potentially curative therapy for localized gastric cancer [see Figure 5]. Cure requires removal of all gross and microscopic disease. More specifically, a margin-negative (R0) resection entails wide local excision of the primary tumor with en bloc removal of all associated lymphatic vessels and any local or regional extension of disease. The downside of surgical resection as a sole modality of therapy is that it has a high rate of relapse. Consequently, several areas of surgical treatment of stomach cancer remain subject to controversy. In particular, the extent of gastric resection, the extent of lymph node dissection, the optimal approach to proximal stomach lesions, and the role of splenectomy and adjacent organ resection continue to generate significant debate. Moreover, recent single-center studies have demonstrated the feasibility of laparoscopic resection, although this approach is still investigational and not considered the standard of care in the United States.40,41

**Extent of gastric resection** R0 resection (i.e., resection of all gross disease with microscopically negative margins) has been shown to have a clear impact on overall survival after potentially curative surgery. In the German Gastric Cancer Study, a prospective multicenter observational trial, the calculated 10-year survival rate in the entire population was 26.3%, compared with 36.1% in patients who underwent an R0 resection.42 In a large multi-institution adjuvant therapy trial, 19% of patients underwent an R1 resection (i.e., had resection-line involvement); only 9% of patients with stage I, II, or III disease...
and resection-line involvement survived beyond 5 years, compared with 27% of those who underwent an R0 resection. Given the propensity of tumor for submucosal spreading, many authors consider proximal margins of 5 to 6 cm, with routine frozen-section analysis, to be optimal. A nomogram has been constructed and validated that predicts disease-specific survival, accounting for various clinicopathologic features after an R0 resection for gastric cancer.

In an effort to lower the positive margin rate, some surgeons have proposed that total gastrectomy be considered the operation of choice for all operable gastric cancers. This approach, originally based on historical data from single institutions, has been tested in three clinical trials. In the first trial, elective total gastrectomy was compared with subtotal gastrectomy as curative intent therapy for adenocarcinoma of the antrum. Elective total gastrectomy did not increase mortality, but it also did not improve 5-year survival (which was 48% in both treatment arms). In the second trial, patients with antral cancer were randomly assigned to undergo either subtotal gastrectomy or total gastrectomy with extended lymph node dissection (ELND) and en bloc distal pancreatectomy and splenectomy. Total gastrectomy was associated with increased operative time, greater transfusion requirements, and longer hospital stay; however, median survival was significantly better in the subtotal gastrectomy group (1,511 days versus 922 days). In the third trial, the investigators concluded that subtotal gastrectomy should be the procedure of choice for cancer of the distal half of the stomach provided that an adequate negative proximal margin can be achieved. This conclusion was based on their finding that 5-year survival was essentially equivalent in the two groups studied (65.3% in the subtotal gastrectomy group versus 62.4% in the total gastrectomy group).

**Options for proximal gastric cancer**

As noted (see above), adenocarcinoma of the gastric cardia and the esophagogastric junction appears to be clinically distinct from adenocarcinoma of the distal stomach, and its incidence is currently escalating across all races and age groups. Accordingly, it is imperative that surgeons understand the surgical options for treatment of proximal gastric cancer.

For tumors originating from the distal esophagus, esophagectomy—either transhiatal esophagectomy with a cervical anastomosis or transthoracic (Ivor-Lewis) esophagectomy with a thoracic anastomosis—is clearly the procedure of choice. For tumors of the cardia, it has been suggested that esophagogastrectomy might offer a survival advantage over total gastrectomy with an esophagojejunal anastomosis. This suggestion was evaluated in a study of 1,002 patients with adenocarcinoma of the esophagogastric junction. The investigators divided tumors into three types on the basis of the location of the tumor center—cancers of the distal esophagus (type I), cancers of the cardia (type II), and cancers of the subcardial fundus (type III)—and analyzed the demographic and long-term survival data. Operative mortality proved to be higher with esophagogastrectomy than with extended total gastrectomy. Furthermore, R0 resection and lymph node status were found to be the dominant prognostic factors influencing survival. Finally, in patients with type II lesions, the pattern of lymphatic spread was primarily to paracardial, lesser curvature, and left gastric node groups. These data, taken together, led the authors to conclude that total gastrectomy is preferable to esophagogastrectomy in this setting if a margin-negative resection can be achieved.

An alternative approach to treating proximal gastric cancer is to perform a proximal subtotal gastrectomy. To date, no prospective studies have compared this method with total gastrectomy or transhiatal esophagogastrectomy for...
Figure 3  Computed tomographic scan of a patient with advanced gastric carcinoma. Water (a negative contrast agent) has been used to distend the stomach. The images were acquired with the patient in the prone position to allow the stomach to fall away from the retroperitoneum and to define the interface between the stomach and the pancreas. The arrows indicate the gastric tumor.

Figure 4  (a) Endoscopic ultrasonographic (EUS) image of a T3 gastric neoplasm. The arrow indicates the gastric tumor infiltrating the stomach wall. (b) EUS reveals the presence of suspicious perigastric (N1) nodes, later confirmed as malignant at operation. The arrow indicates the perigastric lymph node.

Thus, the evidence at present does not support routine performance of total gastrectomy for lesions of the distal fundus or antrum provided that histologically negative margins are achievable without compromise of the gastric inlet. Our current practice is to perform a subtotal gastrectomy with Billroth II reconstruction for tumors of the distal stomach, a total gastrectomy with Roux-en-Y esophagojunostomy for most cancers of the fundus and the proximal stomach, and either a transthoracic esophagogastrectomy or...
Figure 5  Algorithm illustrating the workup and treatment of a patient with gastric carcinoma.  
CBC = complete blood cell count; CT = computed tomography; EUS = endoscopic ultrasonography; 5-FU = 5-fluorouracil.
a transthoracic esophagogastrectomy with gastric interposition for tumors of the esophagogastric junction and the cardia.

**Extent of lymph node dissection**  A Polish-Austrian surgeon, Mikulicz, was one of the first physicians to promote extended lymphadenectomies in gastric cancer because he believed that aggressive locoregional control was necessary to control the stepwise progression of cancer metastases through lymph nodes. Today the debate continues between those surgeons who advocate D2 or D3 resections echoing Mikulicz’s beliefs versus those surgeons who argue that extensive lymphadenectomies only add perioperative morbidity and mortality without improving survival. This discussion is especially relevant in the United States, where the majority of patients diagnosed with gastric cancer who undergo resection are found to have nodal disease. Controversy extends beyond the United States due to the fact that Asian countries have been performing extended lymphadenectomies for many years, whereas Western countries have only recently recommended extended lymphadenectomies (D2) in their guidelines. Gastric lymph node drainage generally follows the vasculature, and the most common lymph node metastases include the lesser curvature (29%), infrapyloric (23%), greater curvature (22%), right cardia (19%), and left gastric artery (19%). Gastric lymph node dissections have traditionally been divided into D1 through D4. A D1 dissection includes removal of the perigastric lymph nodes along the greater and lesser curves of the stomach. A D0 dissection is anything less than a D1 dissection [see Figure 6]. A D2 dissection includes the D1 nodes in addition to nodes along the left gastric, common hepatic, splenic, and left hepatoduodenal arteries. D3 and D4 dissections add lymph nodes in the posterior hepatoduodenal ligament and para-aortic lymph nodes. The extent of lymph node dissection generated much controversy starting in the 1980s, when stage-specific 5-year survival in Japan was shown to be superior to that in the United States, which was theorized to be secondary to the extended lymphadenectomies performed in Japan compared with those performed in the United States. This controversy was a stimulant for several randomized controlled trials evaluating the extent of lymph node dissections in gastric cancer.

Dent and colleagues performed one of the first trials in South Africa in the late 1980s in which they randomized 22 patients to a D1 dissection and 21 patients to a D2 dissection. The researchers found similar 3-year survival although increased morbidity in the D2 dissection group. A larger trial was then performed in the United Kingdom with 400 patients randomized to either a D1 or D2 lymph node dissection. In this trial, those patients with tumors in the middle and upper thirds of the stomach underwent a distal pancreatectosplenectomy to obtain the splenic hilar nodes and retropancreatic nodes. The 5-year survival between the two groups was not statistically significant: 35% in the D1 group versus 33% in the D2 group. Although no overall survival difference was noted, on multivariate analyses, those patients who did not undergo a pancreatectosplenectomy in the D2 group had an increased survival compared with those in the D1 group. A similar trial in the Netherlands randomized 380 patients with gastric cancer to a D1 lymph node dissection and 331 patients to a D2 dissection. As in the previous trial, the 5-year survival rates were not statistically significant between the two groups: 45% in the D1 group and 47% in the D2 group. The study was followed out to 11 years and again did not show a survival benefit for the D2 lymph node dissection. There was a significant increase in postoperative complications (25% versus 43%) and deaths (4% versus 10%) in the D2 group compared with the D1 group as well. It should be noted that with subgroup analysis, those patients with N2 disease seemed to benefit from a D2 dissection and a pancreatectomy/splenectomy was the biggest risk factor for the postoperative morbidity and mortality.

One of the major criticisms of the previous two trials was a lack of surgeon consistency and training in performing D2 dissections. The next trial performed in Italy attempted to address this concern by including specialized surgeon training as part of the study. In this trial, 267 patients with gastric cancer were randomized to a D1 or D2 dissection. As with the previous studies, there was no statistically significant difference in 5-year survival between the two groups: 66.5% in the D1 group and 64.2% in the D2 group. Unlike the other studies, there was no significant difference in morbidity between the D1 and D2 groups (12% versus 18%, respectively) or mortality (3% versus 2.2%, respectively). Subgroup analysis suggested that those patients with T2-T4 tumors and positive lymph nodes benefited from a D2 dissection and had improved 5-year survival rates compared with those in the D1 group: 59% versus 38%.

A randomized trial performed in Taiwan evaluated extended lymphadenectomies and was performed at a single institution with three well-trained surgeons who had each completed at least 25 D3 dissections prior to the study. Patients were randomized to a D1 dissection or a D3 dissection. In this study, a D3 dissection was defined as resection of perigastric lymph nodes along the greater and lesser curves of the stomach. A D3 dissection was defined as resection of additional lymph nodes around the left gastric, common hepatic, and splenic arteries as well as nodes in the hepatoduodenal ligament and retropancreatic lymph nodes. The D3 group demonstrated an increased overall 5-year survival of 60% compared with the D1 group at 53.6%. This implies that a D3 lymph node dissection performed by a well-trained surgeon can offer a survival benefit compared with a D1 dissection. A Japanese study evaluated an even more extensive lymph node dissection known as a para-aortic lymph node dissection (PAND), in which 523 patients with curable gastric cancer were randomized to either the standard D2 dissection or the D2 plus PAND dissection. They found no significant difference in 5-year survival between the D2 and PAND groups (69.2 versus 70.3, respectively). There was a trend toward an increase in complications in the PAND group (28% in the PAND group versus 21% in the D2 group). This implies that the extensive PAND dissection does not provide a benefit for gastric cancer patients.

Current AJCC guidelines state that pathologic examination of at least 15 lymph nodes is required for adequate staging. Specifically, examination of at least 15 nodes is required to confidently deem a patient free of nodal metastases. However, multiple studies have demonstrated inadequate nodal assessment that is somewhat related to hospital type. In an effort to confirm the benefit of this staging system, investigators from the MSKCC reviewed their experience with 1,038 patients who underwent R0 resection for gastric cancer. The location of positive lymph nodes (within 3 cm of the primary tumor versus more than 3 cm away) did not...
significantly affect median survival; however, the number of positive lymph nodes had a profound effect on survival. Furthermore, in cases in which at least 15 nodes were examined (27% of the total), the median survival for patients with metastasis in one to six regional lymph nodes, metastasis in seven to 15 regional lymph nodes, and metastasis in more than 15 regional lymph nodes was significantly longer than the median survival reported in cases in which 14 or fewer nodes were resected with the specimens. These findings are consistent with published data from our own institution, which indicate that the number of positive lymph nodes is a highly significant predictor of survival. In our series of 110 patients, those with seven or more positive lymph nodes had a median disease-free survival (DFS) of 17.6 months, whereas those with six or fewer positive nodes had a median DFS of 44 months. Data from other centers support this view as well.

It is our current practice to perform a D2 lymph node dissection with resection of all perigastric lymph nodes along the greater and lesser curvatures of the stomach, as well as those along the common hepatic artery, the left gastric artery, the celiac axis, and the splenic artery. We make every attempt to preserve the tail of the pancreas and spleen, with multivisceral resection reserved for cases of overt direct extension of malignant disease in the absence of disseminated metastasis. This strategy should provide adequate staging in terms of the AJCC guidelines, minimize morbidity, and possibly confer a survival advantage on certain patient subgroups, as suggested by the results of the trials mentioned.

Routine splenectomy has been proposed as a means of facilitating clearance of metastatic nodes along the splenic artery and in the splenic hilum, but there is little evidence to support this practice in the treatment of proximal gastric cancer. Multiple studies have demonstrated the deleterious effect of splenectomy when it is performed as part of an extended gastric resection. Most studies show no increase in survival rates with splenectomy in patients with gastric cancer, although there tends to be a significant increase in morbidity. The authors concluded that routine splenectomy does not increase survival and should be reserved for situations in which the gastric tumor directly invades the splenic hilum or there is evidence of gross nodal metastases along the splenic artery.

**Figure 6** Gastric lymphadenectomy. A D1 lymphadenectomy includes lymph nodes along the greater and lesser curves of the stomach. A D2 dissection includes the D1 nodes in addition to nodes along the left gastric, common hepatic, splenic, and left hepatoduodenal arteries.
Nonsurgical Therapy

**Endoscopic mucosal resection**  In those patients with EGC, defined as cancer confined to the mucosa or submucosa, EMR is an alternative to gastrectomy. According to the NCCN guidelines, EMR can be considered for lesions less than 2 cm in diameter, is shown on histopathology to be well/moderately differentiated, does not invade beyond the submucosa, does not exhibit lymphovascular invasion, and has clear lateral and deep margins.\(^{39}\) Traditionally, gastric well/moderately differentiated, does not invade beyond the NCCN guidelines, EMR can be considered for lesions less than 3 cm in diameter. One study from Germany that included 39 patients with EGC who were considered to be low risk for EMR (tumor < 2 cm, no invasion of lymph or vessels) demonstrated 97% remission with the initial treatment. Recurrent lesions were found in 29% of the patients and were all successfully treated with repeat EMR.\(^{24}\) A Japanese study evaluated 131 patients with EGC (tumor < 2 cm and no ulcerative change) who underwent EMR between 1978 and 1996.\(^{25}\) The overall 5- and 10-year survival rates were 84% and 64%, respectively, and the disease-specific 5- and 10-year survival rates were both 99%. The overall complication rate in both studies was low. For EMR to be an effective treatment for EGC, routine follow-up and surveillance are a necessity.

**Adjuvant therapy**  Interest in additional therapy beyond surgical resection for gastric cancer stems from the fact that 80% of patients who die from gastric cancer have a local recurrence.\(^{76}\) Several trials have investigated the role of adjuvant chemoradiation in patients with resectable tumors of the stomach or gastroesophageal junction (GEJ). The INT 0116 trial is the largest trial to date, and it used contemporary radiotherapy techniques.\(^{77}\) The trial randomized 556 patients with adenocarcinoma of the GEJ or stomach to surgery plus postoperative chemoradiation or surgery alone. The adjuvant chemoradiation treatment consisted of one cycle of 5-fluorouracil (5-FU) and leucovorin followed 1 month later by 45 Gy of radiation in combination with 5-FU and leucovorin. The chemoradiation group demonstrated an improved median overall survival at 36 months compared with 27 months in the surgery-alone group. The 3-year DFS (48% versus 31%) and overall survival (50% versus 41%) rates were also significantly improved in the chemoradiation group compared with the surgery-alone group. The survival benefit was confirmed out to 10 years.\(^{78}\) The major criticism of this trial was the extent of the surgical resection. Only 10% of the resections were the recommended D2 lymphadenectomy, and the majority (54%) underwent a D0 resection, whereas only 38% underwent a D1 resection.\(^{79}\) This lack of surgical resection likely contributed to falsely elevated failure rates in the surgical arm and concomitantly exaggerated the benefit of adjuvant therapy. This is supported by the fact that the surgery-only group had more local and regional recurrences compared with the adjuvant group (178 versus 101). The Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial provides additional evidence in favor of adjuvant chemoradiation. This trial compared adjuvant chemoradiation with adjuvant chemotherapy alone.\(^{80}\) It included 458 patients with completely resected gastric cancer, including a D2 lymph node dissection, who were assigned to either capecitabine plus cisplatin or capecitabine plus cisplatin followed by chemoradiotherapy (45 Gy). The addition of radiotherapy to the capecitabine did not significantly reduce recurrence rates, although patients with nodal disease had a superior 3-year DFS of 76% compared with 72% receiving chemotherapy alone.\(^{81}\)

**Neoadjuvant therapy**  The standard of care in the United States for gastric cancer has shifted over the years from surgery alone to perioperative chemotherapy or chemoradiation therapy. The NCCN guidelines now recommend neoadjuvant therapy for T2 tumors and higher. Several advantages have been cited for using neoadjuvant treatment. One reason for using neoadjuvant treatment is to “downstage” a tumor prior to resection. This can be especially useful in patients who present with unresectable, nonmetastatic disease, and it gives them a chance to be downstaged enough to undergo a resection. Neoadjuvant therapy also can potentially spare those patients with aggressive disease a morbid operation if they develop metastases while receiving treatment. Those patients with bulky T3/T4 disease, limitis plastica, or visible perigastric nodes on imaging are patients who are high risk for metastases and may not benefit from an operation. A trial of neoadjuvant therapy can further elucidate aggressive tumor biology prior to making operative decisions.

There are several large randomized trials supporting this treatment modality. The most influential and largest trial is the United Kingdom Medical Research Council Adjuvant Gastric Infusion Chemotherapy MAGIC trial, which randomly assigned patients with resectable adenocarcinoma of the stomach (74%), GEJ (11%), or lower esophagus (15%) to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients).\(^{82}\) Resectable cancer was considered stage II or higher with no evidence of metastatic disease or locally advanced inoperable disease as evidenced by ultrasonography, CT, or laparoscopy. Chemotherapy consisted of three cycles of epirubicin, cisplatin, and 5-FU given pre- and postoperatively. The perioperative chemotherapy group had a statistically significant improved survival rate at 5 years of 36% compared with 23% in the surgery-alone group. The local failure rate of the chemotherapy group was 14% compared with 21% in the surgery-alone group. Both treatment groups had similar complication rates and 30-day mortality. One major limitation of this study (and many neoadjuvant therapies) is that only 42% of the perioperative chemotherapy group received the postoperative chemotherapy treatment.

A similar trial was carried out in a French multicenter trial (FNCLCC/FFCD trial) that included patients with resectable adenocarcinoma of the stomach (n = 144), and distal esophagus (n = 25).\(^{83}\) This trial randomized 113 patients to perioperative chemotherapy and 111 patients to surgery alone. The chemotherapy regimen in this trial consisted of two or three cycles of cisplatin and 5-FU preoperatively and three or four cycles postoperatively. The perioperative chemotherapy group demonstrated a significantly improved 5-year survival of 38% compared with the surgery-alone group at 24%. There was also an improved curative resection rate of 84% in the perioperative chemotherapy group.
compared with 73% in the surgery-alone group. A key difference in this trial compared with the MAGIC trial is the patient populations. In the MAGIC trial, a higher proportion of the patients (74%) had gastric cancer, compared with this trial, in which only 25% had gastric cancer.

A recent Japanese trial provides evidence of a beneficial oral fluoropyrimidine, S-1, used as an adjuvant treatment for East Asian patients with curatively resected gastric cancer. S-1 is a combination of three different agents: flortafur (tegafur), gimeracil, and oteracil. In this randomized trial, patients in Japan with stage II or III gastric cancer who underwent curative resection with a D2 lymph node dissection were assigned to either surgery followed by S-1 treatment (529 patients) or surgery alone (530 patients). The S-1 treatment group demonstrated statistically significant improved 5-year survival of 72% compared with 61% in the surgery-alone group. The results of this trial have led to 1 year of postoperative S-1 treatment as the standard of care for East Asian patients with gastric cancer. It is difficult to extrapolate this data to non-Japanese patient populations as the 5-year survival rates in this trial (in both treatment groups) were far superior than those in non-Japanese trials.

Implementation of consensus guidelines for gastric cancer treatment

It is evident that surgery alone is insufficient treatment for locally advanced gastric cancer, and consensus guidelines such as the NCCN recommend preoperative chemoradiation therapy for localized GEJ adenocarcinoma and perioperative chemotherapy or postoperative chemoradiation therapy for localized gastric adenocarcinoma. These recommendations are based on the results of the previously mentioned trials, namely the MAGIC trial, INT-0116 (Macdonald) trial, and the French multicenter trial, which all demonstrated improved survival with perioperative chemotherapy. These trials were published in the early 2000s, but it has been unclear as to how these results were implemented into clinical practice outside the auspices of a trial. Sherman and colleagues determined the impact of these studies and guidelines by identifying 30,448 patients from the National Cancer Data Base who underwent surgical resection for stage IB-IIIA gastric adenocarcinoma between 1998 and 2007. Of those patients with stage IB-IIIA gastric adenocarcinoma, the proportion who received systemic therapy either pre- or postoperatively increased from 35.7 to 61% from 1998 to 2007, and concomitantly, the proportion of patients undergoing surgery alone significantly decreased between those years. The largest increase occurred between 1999 and 2000, which coincided with the release of the INT-0116 data. The most predictive factor for receiving neoadjuvant therapy was tumor location in the gastric cardia.

FOLLOW-UP AND MANAGEMENT OF RECURRENT DISEASE

Even after gross resection of all disease with microscopically negative margins (R0 resection), recurrence of gastric carcinoma is common. Adenocarcinoma of the stomach may spread through direct extension, via lymphatic channels to regional and distant lymph nodes, or via the bloodstream to distant sites. Furthermore, once tumors have penetrated the serosa (T3), peritoneal metastasis becomes a possibility. Through autopsy series and clinical studies, certain definite patterns of locoregional failure and distant metastasis have been established. Locoregional recurrences are common in the gastric bed and the adjacent lymph nodes. Clinical and reoperative evaluations have documented recurrent disease at the anastomosis, in the retroperitoneum, or in the regional lymph nodes in 3 to 69% of patients; the incidence of recurrence may vary depending on whether the patients had received adjuvant therapy. One autopsy series documented a locoregional recurrence rate of 94% in patients treated with surgery alone. The peritoneum is ultimately involved in 17 to 50% of all patients. The most common sites of visceral metastases are the liver and the lungs.

In view of the high recurrence rates, all patients who have undergone resection should be seen for routine surveillance examinations. Currently, the NCCN recommends that a complete history and physical examination be conducted every 3 to 6 months for 1 to 3 years, every 6 months for 3 to 5 years, and then annually thereafter. A complete blood count, serum electrolyte concentrations, imaging studies (e.g., CT), and endoscopy should be done if clinically indicated, usually in response to new symptoms. In addition, long-term vitamin B12 supplementation should be initiated for patients who have undergone a proximal or subtotal gastrectomy.

Nonadenocarcinomatous Gastric Malignancies

GASTRIC LYMPHOMA

Gastric lymphoma is the second most common malignancy of the stomach, accounting for 2 to 9% of gastric tumors in the United States. Lymphomas of the stomach are of the non-Hodgkin lymphoma (NHL) type. The stomach is the most common site of extranodal involvement of NHL and accounts for nearly 50% of all such cases.

Clinical Evaluation

The presenting symptoms of gastric lymphoma, like those of gastric adenocarcinoma, are nonspecific and include loss of appetite, weight loss, vomiting, and bleeding. B symptoms (e.g., fever and night sweats) are relatively rare: in one multicenter trial concerned with primary gastric lymphoma, they occurred in fewer than 12% of patients enrolled. Risk factors for gastric lymphoma include H. pylori infection, immunosuppression after solid-organ transplantation, celiac disease, inflammatory bowel disease, and HIV infection.

Investigative Studies

The diagnosis is most frequently established by means of endoscopy with biopsy. Staging studies include a comprehensive blood count, a lactate dehydrogenase level, and a comprehensive chemistry panel; CT of the chest, abdomen, and pelvis; and, often, a bone marrow biopsy. All pathology slides should be reviewed by an experienced hematopathologist.

Staging and Prognosis

Numerous staging systems have been employed to stage NHL of the GI tract. Of these, the one most commonly applied is a modification of the Ann Arbor staging system for lymphoma. For surgeons, the most important determination is often whether the NHL (1) is confined to the stomach and the perigastric nodes (stage I and II disease), (2)
involves other intra-abdominal nodes and organs (stage III), or (3) extends outside the abdomen (stage IV).89

Management

Over the past decade, the management of patients with gastric lymphoma has undergone significant changes. Generally, there has been a shift away from surgical management, even in relatively localized cases (stages I and II).90 This shift is the result not only of the documented success of chemotherapy alone for more advanced cases (stages III and IV) but also of a better understanding of the etiology of gastric lymphoma.91 Approximately 45% of all gastric lymphomas are low-grade mucosa-associated lymphoid tissue (MALT) lymphomas.86 The gastric mucosa is normally devoid of lymphoid tissue. It is hypothesized that MALT develops in the stomach in response to chronic H. pylori infection.82

Numerous trials have documented the efficacy of anti–H. pylori therapy, with complete remission rates ranging from 50 to 100%.87,95 Low-grade lymphomas that are more advanced or do not regress with antibiotic therapy may be treated with combinations of H. pylori eradication, radiation, and/or combination chemotherapy.86 For localized persistent disease, modest doses of radiation, on the order of 30 Gy, may be employed. When chemotherapy is required, multiagent regimens, such as cyclophosphamide-vincristine (Oncovin)-prednisolone (COP), are often used. High-grade lymphomas are often treated with chemotherapy and radiation therapy according to the extent of disease. The cyclophosphamide-hydroxydoxorubicin-vincristine (Oncovin)-prednisolone (CHOP) regimen is the one most frequently employed. In some studies, the anti-CD20 monoclonal antibody rituximab has been either added to standard therapy or used alone, with encouraging results.89

Surgical resection, once thought to be essential for the diagnosis, staging, and treatment of early-stage gastric lymphoma, is now used mainly in patients who experience bleeding or perforation. In the German Multicenter Study Group trial, 185 patients with stage I or II gastric lymphoma were treated either with gastrectomy followed by radiation or (in the case of high-grade lesions) chemotherapy plus radiation or with chemotherapy and radiotherapy alone.87 There was no significant difference in survival between the group receiving surgical treatment and the group receiving nonoperative therapy: overall 5-year survival rates were 82.5 and 84%, respectively. There were no perforations and only one hemorrhage (in a patient treated with chemotherapy alone).

Currently, patients with gastric lymphomas are treated primarily with chemotherapy or radiation therapy; only rarely do they require surgical intervention for complications encountered during therapy.

GASTROINTESTINAL STROMAL TUMOR

Gastrointestinal stromal tumor (GIST), although relatively rare in absolute terms, is the most common sarcoma of the GI tract,86 with approximately 6,000 cases reported each year in the United States alone. The stomach is the most common site of involvement, accounting for 60 to 70% of cases;86 the small intestine (25%), the rectum (5%), the esophagus (2%), and a variety of other locations account for the remainder. On the basis of their appearance on light microscopy, GISTs were once thought to be of smooth muscle origin, and most were classified as leiomyosarcomas.89 Thus, extended gastric resection, often including contiguous organs, was advised. Recurrence developed after R0 resection in approximately 50% of cases.89 With the advent of immunohistochemistry and electron microscopy, it became clear that GIST has both smooth muscle and neural elements, and the cell of origin is now believed to be a precursor of the interstitial cells of Cajal, an intestinal pacemaker cell.100 The diagnosis of GIST is secured by immunohistochemical staining for the tyrosine kinase receptor KIT (CD117), which highlights the presence of interstitial cells of Cajal. More than 95% of GISTs exhibit unequivocal staining for KIT.97 Approximately two thirds of GISTs also express CD34. Histologically, these tumors may exhibit a spindle cell pattern, an epithelioid pattern, or a mixed subtype.

Clinical Evaluation

The median age at incidence is 63 years, and tumors are generally between 0.5 and 4 cm in diameter at the time of diagnosis (median diameter 6 cm).102 Mass-related symptoms (e.g., abdominal pain, bloating, and early satiety) may be present. Melena or anemia from overlying mucosal ulceration may be present as well. A small subset of patients have peritonitis as a consequence of tumor rupture and subsequent hemorrhage. Finally, many GISTs are discovered incidentally during operation, abdominal imaging, or endoscopy.

Investigative Studies

When a GIST is suspected, abdominal and pelvic imaging with either CT or magnetic resonance imaging (MRI) is indicated [see Figure 7]. Chest imaging is performed as well. Endoscopy, with or without EUS, may occasionally help with surgical planning, but because of the infrequency of mucosal involvement, it is rarely diagnostic.99 Surgical consultation should be obtained to determine whether the lesion can be resected with acceptable morbidity. If the tumor is resectable, biopsy should not be performed, because of the risk of tumor rupture and intra-abdominal dissemination. Biopsy may be required, however, if the patient has widespread disease or may be enrolling in a trial of neoadjuvant therapy. In such cases, biopsy may be performed percutaneously or at the time of EUS.

Staging and Prognosis

Although the majority of gastric GISTs have a benign course, a wide spectrum of biologic behavior has been observed. Of the prognostic factors examined to date, tumor size and mitotic rate appear to be the most valuable. If the tumor is less than 2 cm in diameter and the mitotic count is lower than five per high-power field (HPF), the risk of an aggressive disease course is considered to be very low. Conversely, if the tumor is larger than 10 cm, if the mitotic count is higher than 10/HPF, or if the tumor is larger than 5 cm with a mitotic count higher than five/HPF, the risk of aggressive clinical behavior is considered to be high. For all other tumors, the risk of aggressive disease is considered to be intermediate.99 The site of the primary tumor has also been shown to be important, with gastric GISTs having a better prognosis compared with small bowel GISTs of comparable size and mitotic rate.104 In addition, the most recent
version of the AJCC Cancer Staging Manual (7th Edition) has an added staging system for GISTs [see Table 3 and Table 4].

**Management**

**Surgical therapy**  The role of surgery in the treatment of a GIST is to resect the tumor with grossly negative margins, leaving the pseudocapsule intact [see Figure 7]. Lymph node involvement is rare with GISTs; thus, no effort is made to perform ELND. The tumor must be handled with care to prevent intra-abdominal rupture. Formal gastric resection is rarely required: as a rule, it is indicated only for lesions in close proximity to the pylorus or the esophagogastric junction. The NCCN has guidelines updated annually specifically for the management of GISTs.

**Nonsurgical therapy**  If the tumor has metastasized or has advanced locally to the point where surgical therapy would result in excessive morbidity, the patient is treated with the tyrosine kinase inhibitor imatinib mesylate. Imatinib is a selective inhibitor of a family of protein kinases that includes the KIT receptor tyrosine kinase, which is expressed in the majority of GISTs. Originally indicated for the treatment of chronic myelocytic leukemia, imatinib was approved for the treatment of KIT-positive GIST in 2002, when phase II clinical trials documented sustained objective responses in a majority of patients with advanced unresectable or metastatic GIST. Patients with borderline resectable lesions should be treated with imatinib until they exhibit a maximal response as documented by CT and positron emission tomography (PET); surgery may then be undertaken to resect any residual foci of disease. Similarly, although patients with metastatic disease are unlikely to manifest a complete response to imatinib therapy, they should be periodically reevaluated and considered for resection should surgical treatment become technically feasible.

In 2009, the results of the American College of Surgeons Oncology Group (ACOSOG) phase III trial (Z9001) were reported. After resection of intermediate-risk GIST, patients were randomized to treatment with 1 year of imatinib (400 mg/day) versus placebo. Adjuvant imatinib was well tolerated. After a median follow-up of 19.7 months, patients treated with imatinib had a considerably better recurrence-free survival compared with the placebo group (98% versus 83%, \( p < 0.001 \); hazard ratio 0.35). After resection of a GIST, adjuvant imatinib is recommended for patients with moderate-to-high risk of recurrence.

Longer duration of imatinib was evaluated by the Scandinavian Sarcoma Group (SSG) XVIII trial, which compared 36 months versus 12 months of adjuvant imatinib in patients with high-risk resected GIST. High risk was defined as having at least one of the following: tumor size greater than 10 cm in diameter, mitotic count greater than 10/50 HPF, tumor size greater than 5 cm with a mitotic rate greater than five/HPF, or tumor rupture. In those patients treated with 36 months of imatinib, there was a significant improvement in overall 5-year survival of 92% compared with 82% for the 12-month treatment group. The 5-year recurrence-free survival was also significantly improved: 66% in the 36-month group and 48% in the 12-month group. There were more grade 1 and 2 treatment-related adverse events in the 36-month group, although the grade 3 and 4 events were similar in both groups. This study established 36 months of adjuvant imatinib as standard of care in high-risk patients with GIST.

**Gastric Carcinoid**

Gastric carcinoid tumors are rare, but this incidence is increasing. These tumors now account for approximately 10% of all GI carcinoids and 2% of all gastric tumors. The median age at diagnosis is 64, and the tumors are somewhat more common in women than in men.

**Clinical Evaluation and Investigative Studies**

Gastric carcinoid tumors are often discovered during endoscopic examination of patients experiencing chronic abdominal pain; patients may also complain of vomiting and diarrhea. These tumors are rarely associated with symptoms of the carcinoid syndrome. Diagnosis is usually confirmed by endoscopic biopsy, and EUS is helpful in determining the extent of gastric wall penetration and the degree of regional lymph node involvement.

Gastric carcinoid tumors have been divided into three types, primarily on the basis of their association (or lack thereof) with hypergastrinemia. Type I tumors are associated with chronic atrophic gastritis, are generally small (< 1 cm), and are often multiple and polyloid. They grow slowly and only rarely metastasize to regional nodes or distant sites. Type II tumors are associated with the Zollinger-Ellison syndrome and multiple endocrine neoplasia type I and, like type I tumors, are usually small and multiple. They also grow slowly but are more likely to metastasize than type I gastric carcinoids. Type III (sporadic) gastric carcinoid tumors are the most biologically aggressive type. They are often large (> 1 cm) at the time of diagnosis and are not associated with hypergastrinemia. Type III lesions frequently metastasize to regional nodes (54%) or the liver (24%).

**Management**

For patients with small, solitary type I tumors, endoscopic polypectomy or open resection via gastrotomy (local excision) is the procedure of choice. For patients with multiple or recurrent tumors, antrectomy is indicated to remove the source of the hypergastrinemia only if the patient’s gastric acid secretions are not controlled by proton pump inhibitors. For patients with type II lesions, treatment is similar to that for patients with type I lesions, with the extent of gastric resection determined by the size and number of lesions. For patients with type III lesions, however, either distal or total gastrectomy with ELND is required. All patients undergoing a less than total gastrectomy should be followed with serial endoscopy at regular intervals.

**Small Bowel Malignancies**

Malignant tumors of the small intestine are rare, accounting for fewer than 5% of all GI tract malignancies. In the United States, approximately 6,000 new cases of small bowel cancer are reported each year. The majority of small bowel malignancies are carcinoid tumors, adenocarcinomas, or lymphomas, although GISTs are being noted with increasing frequency in the small intestine. Although adenocarcinomas had traditionally been the most common tumor of the small bowel, a recent report from our group has shown that
Patients has suspected GIST
Obtain CT or MRI of abdomen/pelvis; consider chest imaging.

Tumor is resectable
Assess size.

Less than 2 cm
Assess risk on EUS.

No high-risk EUS features
Consider endoscopic surveillance.

High-risk EUS features
Resect tumor.

Tumor is not resectable; locally advance or metastatic
Obtain biopsy to confirm GIST.

Greater than 2 cm
Assess location.

Away from pylorus
Resect with grossly negative margins and intact pseudocapsule.

Near pylorus or GE junction
May need formal gastric resection.

Obtain biopsy to confirm GIST.

Tumor is not resectable; locally advance or metastatic
Treat with imatinib
Evaluate response with repeat imaging (CT and PET) to determine resectability.

Postresection (RO)
Assess risk based on final pathology.

Tumor is resectable
Surgery if feasible.

Low risk
No further treatment; routine surveillance.

Intermediate/high risk
Treatment with adjuvant imatinib for 1–3 years based on risk factors.

Tumor is not resectable
Continue imatinib until toxicity or disease progression.

Figure 7  Algorithm illustrating the workup and treatment of a gastrointestinal stromal tumor (GIST). High-risk endoscopic ultrasound (EUS) features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity. CT = computed tomography; GE = gastroesophageal; MRI = magnetic resonance imaging; PET = positron emission tomography; RO resection = complete removal of all tumor and microscopically confirmed negative margins.

Scientific American Surgery

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Table 3  American Joint Committee on Cancer
TNM Clinical Classification of Gastrointestinal Stomal Tumors, 7th Edition

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<tr>
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GIST = gastrointestinal stromal tumor.

Table 4  American Joint Committee on Cancer
Staging of Gastric and Small Bowel GISTs, 7th Edition

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Table 5  American Joint Committee on Cancer
Staging of Gastric and Small Bowel Lymphomas, 7th Edition

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GIST = gastrointestinal stromal tumor.

the incidence of carcinoid tumors has increased over the past 20 years, and carcinoids are now the most common tumor of the small intestine.113 Treatment of lymphomas, carcinoid tumors, and GISTs in the small bowel is nearly identical to treatment of the same lesions in the stomach [see Nonadenocarcinomatous Gastric Malignancies, above] and thus are not covered further in this review. Our focus here is on the presentation, diagnosis, and treatment of adenocarcinoma of the small bowel [see Table 3 and Table 6].

CLINICAL EVALUATION

Between 46 and 55% of small bowel adenocarcinomas occur in the duodenum and approximately 13% occur in the ileum.34,105,112–113 Patients frequently present with nausea, vomiting, abdominal pain, weight loss, and GI bleeding; occasionally, they present with iron deficiency anemia or a positive fecal occult blood test result. In rare cases, small bowel obstruction, often with the tumor serving as a lead point for intussusception, is the first manifestation of the disease.114

INVESTIGATIVE STUDIES

When an adenocarcinoma is located in the duodenum, the diagnosis is often made by means of esophagastroduodenoscopy (EGD). Lesions within the first 100 cm of the small bowel may be evaluated with push enteroscopy. When the adenocarcinoma is situated elsewhere in the small bowel, it is localized with small bowel radiographs. Some authors consider enteroclysis to be superior to the more commonly used small bowel follow-through in this setting in that enteroclysis is better able to demonstrate fine mucosal detail.114 In experienced hands, enteroclysis may therefore be more sensitive.115 Some lesions are identified when CT or MRI is performed to evaluate complaints of abdominal pain. Furthermore, abdominal imaging may yield complementary staging information (e.g., the presence of regional adenopathy or metastatic disease). One new method for the identification of small bowel tumors is wireless capsule endoscopy.116 This minimally invasive technique may be particularly useful in identifying small lesions in the distal jejunum and ileum that cannot be identified radiographically.

MANAGEMENT

Aggressive surgical resection remains the cornerstone of therapy for adenocarcinoma of the small intestine.117 For periampullary lesions, pancreaticoduodenectomy is typically required to achieve a margin-negative resection. For lesions in the distal duodenum, a segmental sleeve resection with a duodenojjunostomy is appropriate. For lesions in the jejunum or the ileum, segmental resection may be performed with a wide mesenteric resection to encompass potentially involved regional lymph nodes. Contiguous organs are resected en bloc as necessary.107

Because the presenting signs and symptoms are often vague and nonspecific, diagnosis is often delayed. In one series, only six (11%) of the 53 patients were suspected of having a small bowel tumor at admission.118 In a retrospective review of patients with small bowel tumors treated at our institution, the mean duration of symptoms before surgical management was 110 months, and more than 50% of the patients were found to have stage III or IV disease.111 In our work with the National Cancer Data Base, we found that only 24% of patients presented with metastatic disease.113

The 5-year survival rate continues to be low (24 to 37%).115,118–121 Significant predictors of good overall survival include location in the jejunum, complete (R0) resection, low-grade tumors, and low AJCC tumor stage.119,120–121 The available evidence indicates that all patients with small bowel neoplasms should be offered an oncologically sound surgical resection. In one series, curative (R0) resection was accomplished in 51% of cases.113 No prospective data are available.
available regarding adjuvant therapy, but the treatments and results for colon adenocarcinoma are often extrapolated to small bowel adenocarcinomas.

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References


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11/15


89. Talamonti MS. Gastric cancer. Philadelphia Lippincott Williams & Wilkins; 1998.


