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 may be linked to better refrigeration and a concomitant decrease in the intake of salted, pickled, smoked, and chemically preserved foods; however, this link remains controversial. 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 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 23% for the period extending from 1992 to 1999. This result is probably related to the advanced stage at which most patients present. A 1995 study from the Commission on Cancer of the American College of Surgeons (ACS) found that 66% of patients with gastric cancer presented with locally advanced or metastatic disease. Resection rates ranged from 30% to 50%, and 5-year survival rates after resection with curative intent were directly related to stage at presentation. For stage I disease, the survival rate was 43%; for stage II, 37%; for stage III, 18%; and for stage IV, 20%.

Another relevant change in the epidemiology of gastric cancer is a shift in the distribution of primary lesion sites within the stomach. In the first quarter of the 20th century, two thirds of gastric cancers were located in the antrum and the prepyloric area, and only 10% arose in the cardia or the esophagogastric junction. Since the 1970s, however, adenocarcinoma of the proximal stomach has become increasingly common. In one study, the incidence of adenocarcinoma of the gastric cardia rose from 29.1% to 52.2% in the period between 1984 and 1993. In another, which included 18,365 gastric cancer patients from ACS-approved hospitals, a full 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's 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. 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 have 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 actual 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 greater risk (which may be part of the reason for the reduced risk of gastric cancer associated with diets rich in fruits and vegetables). Accordingly, in most large series, fiberoptic endoscopy with biopsy has replaced contrast radiography as the primary diagnostic technique. 

The primary goal in the evaluation of gastric cancer patients is to stratify them into two clinical stage groups: those with loco-regional 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

### Investigative Studies

Until comparatively recently, an upper gastrointestinal 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 (i.e., 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 biopsy specimens 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) [see Tables 1 and 2]. 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 loco-regional 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

### Table 1 American Joint Committee on Cancer TNM Clinical Classification of Gastric Carcinoma

<table>
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### Table 2 American Joint Committee on Cancer Staging System for Gastric Carcinoma

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the Internet (http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf) and are updated annually. Multidisciplinary evaluation is recommended for all patients. A careful history is obtained and a thorough physical examination performed, with special attention paid 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 of the abdomen and pelvis.

Whereas 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 1]. Nevertheless, CT is still limited in its ability to evaluate peritoneal disease and liver metastases smaller than 5 mm.

Given the limitations of CT, we believe that 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 (which would be considered M1 disease) [see Figure 2]. EUS is unique among imaging modalities in its ability to image the gastric wall as a five-layer structure, with each layer correlating with an actual 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

Figure 1  Shown are CT scans of a patient with a T3 carcinoma involving the posterior wall of the gastric antrum, taken with the patient supine (a) and prone (b). By placing the patient in the prone position and distending the stomach with water, better definition of the extent of the tumor and clearer delineation of the interface between the stomach and the pancreas is achieved.

Figure 2  (a) Shown is an EUS image of a T3 gastric neoplasm. (b) EUS reveals the presence of suspicious perigastric (N1) nodes, later confirmed as malignant at operation.
size larger than 1 cm. In one study comparing preoperative findings from EUS with pathologic findings at operation, EUS was 100% sensitive for N0 disease and 66.7% sensitive for N1 disease. EUS also allows identification and aspiration of small-volume ascites. If cytologic study of the ascitic fluid so obtained 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 accept-
ed as superior to conventional CT in the regional staging of gastric cancer.9

Role of Laparoscopy

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.39 In these situations, there is little to be gained from attempts at palliative resection.

Staging laparoscopy [see 5:20 Gastric and Duodenal Dis.] 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, though derived from relatively small single-institution experiences, are compelling, and they have led the NCCN to encourage laparoscopic staging strongly, either before or at the time of the planned resection.39

MANAGEMENT

Surgical Therapy

Surgical resection [see 5:20 Gastric and Duodenal Dis.] remains the only potentially curative therapy for localized gastric cancer [see Figure 3]. 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 is associated with 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.

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.40 In a large multi-institutional 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.41 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.42,43

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.44 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.45 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 could be achieved.46 This conclusion was based on their finding that 5-year survival probabilities were 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,47 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.48

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 [see 4:7 Open Esophageal Procedures]. For tumors of the cardia, it has been suggested that esophagogastrectomy might offer a survival advantage over total gastrectomy with an esophagojejunostomy anastomosis. This suggestion was evaluated in a study of 1,002 patients with adenocarcinoma of the esophagogastric junction.49 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 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 esophagogastric junction tumors, but surgeons from MSKCC have published their retrospective experience with 98 patients who underwent either total gas-
trectomy or proximal subtotal gastrectomy for proximal gastric cancer over a 10-year period. There were no significant differences between the groups with respect to morbidity, mortality, or 5-year survival. It remains to be seen whether such excellent results can be achieved at other centers.

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 esophageojjunostomy for most cancers of the fundus and the proximal stomach, and either a transthoracic esophagogastrectomy or a transhiatal esophagogastrectomy with gastric interposition for tumors of the esophagogastric junction and the cardia.

Extent of lymph node dissection Over the past decade, few topics in the surgical literature have generated more debate than the optimal extent of regional lymphadenectomy for gastric cancer. In Japan, where radical surgery for gastric cancer is now universally accepted, the JRSGC has codified the extent of lymphatic dissection according to the level of nodes dissected. A D1 lymph node dissection involves resection of the perigastric lymph nodes along the greater and lesser curvature of the stomach. A D0 dissection is anything less than a D1 dissection. A D2 dissection entails resection of the D1 nodes along with nodes along the common hepatic artery, the left gastric artery, the celiac axis, and the splenic artery. A D3 lymph node dissection adds resection of nodes in the hepatoduodenal ligament and the root of the mesentery. Finally, a D4 resection calls for a D3 dissection plus resection of the retroperitoneal para-aortic and paracolic lymph nodes. The JRSGC defines a curative operation as a gastric resection that includes lymph nodes one level beyond the level of pathologic nodal involvement. Thus, in Japan, a D2 lymph node dissection is considered the standard resection for even relatively early cancers, and numerous studies have cited the benefits of D3 and even D4 lymphadenectomy for advanced carcinoma.

Western surgeons have been reluctant to embrace radical lymphadenectomy, arguing that it has yet to demonstrate an unequivocal survival advantage in any prospective, randomized trial from a Western institution or cooperative group. Detractors further argue that the survival advantage associated with more radical procedures simply reflects stage migration, a higher incidence of early gastric cancers, and differences in tumor biology and body habitus between Japanese and Western populations, and they point to the increases in operating time and morbidity that often accompany extended gastric resections. One retrospective review of the tumor registries of over 2,000 hospitals in the United States found that D2 lymph node dissection had no survival advantage over D1 lymph node dissection in terms of either the median survival time or the 5-year survival rate.

Two prospective trials from Western Europe examined this issue further in an effort to evaluate the safety and efficacy of ELND. In the Dutch Gastric Cancer Group trial, 711 patients were randomly assigned to undergo either D1 or D2 lymphadenectomy as part of a potentially curative gastrectomy for biopsy-proven adenocarcinoma. This trial was unique in its use of extensive quality control measures, which included instruction and operative supervision by an expert gastric cancer surgeon from Japan (who also assisted with the processing and pathologic examination of the surgical specimens). Patients without evidence of disseminated metastases underwent either total gastrectomy or, if 5 cm proximal margins could be obtained, distal gastrectomy. In this study, a D2 lymph node dissection entailed distal pancreatectomy and splenectomy. Both morbidity and mortality were significantly higher in the D2 group than in the D1 group, and D2 dissection conferred no demonstrable survival advantage at a median follow-up of 72 months.

In a trial from the Medical Research Council in the United Kingdom, 400 patients with stage I to IIB disease were randomly assigned to undergo either a D1 or a D2 lymph node dissection. There was no significant difference in overall 5-year survival between the two arms, but multivariate analysis demonstrated that clinical stages II and III, advanced age, male sex, and removal of the pancreas and the spleen were independently associated with poor outcome. The authors concluded that the classic Japanese D2 dissection offered no survival advantage over D1 dissection. However, they hypothesized that D2 dissection with preservation of the distal pancreas and the spleen might lead to decreased morbidity and mortality within the extended resection group and thus potentially to superior outcomes.

Further support for this hypothesis was provided by two non-randomized trials from specialized centers. The Italian Gastric Cancer Study Group (IGCSG) completed a phase II multicenter trial designed to evaluate the safety and efficacy of pancreas-preserving D2 lymph node dissection. Quality control measures included supervision by a surgeon who had studied the technique of D2 lymph node dissection at the National Cancer Center Hospital in Tokyo. At a median follow-up time of 4.38 years, the overall morbidity rate for D2 dissection in the 191 patients enrolled was 20.9%, and the in-hospital mortality was 3.1%. The 5-year survival rate for eligible patients was 55%. In a prospective series of 125 patients undergoing standardized D2 lymph node dissection at a single Western center, the investigators reported a mortality of 1.37% and an overall morbidity of 33.5%. As in the IGCSG study, distal pancreatectomy was avoided in all cases, except when direct extension was suspected on the basis of macroscopic findings (5.5% of cases). Overall 5- and 10-year survival rates for this highly selected cohort were 52.3% and 40%, respectively. These studies suggest D2 lymph node dissection may be safely performed in Western centers, when accompanied by careful selection of patients, strict standardization of technique, and a strategy of pancreatic preservation.

Current AJCC guidelines state that pathologic examination of at least 15 lymph nodes is required for adequate staging. In an effort to confirm the benefit of this staging system, investigators from 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 N1 (metastasis in one to six regional lymph nodes), N2 (metastasis in seven to 15 regional lymph nodes), and N3 disease (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 (Northwestern University Feinberg School of Medicine), which indicate that the number of positive lymph nodes is a highly significant predictor of survival. In our series of 110 patients, those with N2 or N3 disease (seven or more positive lymph nodes) had a median disease-free survival (DFS) of 17.6 months, whereas those with
The results of the trials mentioned.

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 [see 5.20 Gastric and Duodenal Dis.]. 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.

Role of splenectomy 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 cancers. Indeed, numerous studies have documented the deleterious effect of splenectomy when it is performed as part of an extended gastric resection.

In a retrospective study of 392 patients who underwent curative gastrectomy at a high-volume cancer center, the impact of splenectomy on survival and postoperative morbidity was evaluated. More significantly, the 5-year observed survival rate was 27 months, compared with 36 months in the surgery-chemoradiation group. In addition, the 3-year survival rate was 41% in the splenectomy group, compared with 21% in the nonsplenectomy group. In other words, the odds ratio for death in the treated group was 0.8, corresponding to a relative risk of 0.94. This result did not, however, reflect a statistically significant improvement. Most oncologists have now abandoned the use of chemotherapy by itself in the adjuvant setting.

In an effort to derive greater therapeutic benefit than can be achieved with either radiation therapy or chemotherapy alone, combinations of the two have been used in the adjuvant setting. In Intergroup Trial 0116, 556 patients who had undergone R0 resection of adenocarcinoma of the stomach or the esophagogastric junction were randomly assigned to treatment with either surgery alone or surgery plus postoperative chemoradiotherapy. Patients with tumors ranging from stage IB to stage IVM0 were included; the majority had T3 tumors and node-positive disease. The therapeutic regimen consisted of 5-FU and leucovorin administered concomitantly with 45 Gy of external-beam irradiation over a period of 5 weeks. Median overall survival in the surgery-only group was 27 months, compared with 36 months in the surgery-chemoradiation group. In addition, the 3-year survival rate was 41% in the

Table 3 Survival after Curative Resection of Gastric Cancer According to AJCC Lymph Node Status

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<td>258 (54)</td>
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<td>137 (29)</td>
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routine splenectomy does not increase survival, and it 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.

Nonsurgical Therapy

Adjuvant therapy As noted (see above), the majority of patients who present with gastric carcinoma and undergo potentially curative surgical treatment will experience locoregional failure, distant metastasis, or both and will succumb to their disease. Accordingly, numerous adjuvant approaches—including chemotherapy, radiotherapy, chemoradiation, immunochemotherapy, and intraperitoneal chemotherapy—have been tried in gastric cancer patients with the aim of improving overall survival and DFS. The results, for the most part, have been disappointing.

Results from prospective, randomized, controlled trials of adjuvant radiation therapy in this setting have failed to establish a survival benefit. In a multi-institutional trial from 1994, patients were randomly assigned to undergo surgery alone, surgery plus adjuvant radiation, or surgery plus adjuvant multiagent chemotherapy. There was no significant benefit to either adjuvant regimen: overall 5-year survival was 20% for surgery alone, compared with 12% for surgery plus radiation therapy and 19% for surgery plus chemotherapy.

Results from trials of chemotherapy alone have been equally unsatisfactory. Because of the established inefficacy of single-agent 5-fluorouracil (5-FU) therapy, combination chemotherapy regimens have been employed. Such regimens have included nitrogen mustard compounds, mitomycin-C, anthracyclines, and members of the cisplatin family. In a meta-analysis of 13 trials comparing adjuvant chemotherapy with observation in non-Asian countries, the odds ratio for death in the treated group was 0.8, corresponding to a relative risk of 0.94. This result did not, however, reflect a statistically significant improvement. Most oncologists have now abandoned the use of chemotherapy by itself in the adjuvant setting.

In a randomized, prospective trial, early and late results of total gastrectomy alone were compared with those of total gastrectomy plus splenectomy in patients being treated for cancers of the upper third of the stomach. All patients underwent a D2 lymph node dissection. The operative mortalities and the 5-year survival rates were similar in the two groups, but the splenectomy group had more infectious complications. Specifically, the splenectomy group had higher incidences of pulmonary complications, postoperative fever higher than 38°C (100°F), and subphrenic abscess formation. We agree with the conclusions of the authors of this study: N0 or N1 disease (six or fewer positive nodes) had a median DFS of 44 months. Data from other centers support this view as well [see Table 3].

The results from prospective, randomized, controlled trials of adjuvant chemotherapy alone have been equally unsatisfactory. Because of the established inefficacy of single-agent 5-fluorouracil (5-FU) therapy, combination chemotherapy regimens have been employed. Such regimens have included nitrogen mustard compounds, mitomycin-C, anthracyclines, and members of the cisplatin family. In a meta-analysis of 13 trials comparing adjuvant chemotherapy with observation in non-Asian countries, the odds ratio for death in the treated group was 0.8, corresponding to a relative risk of 0.94. This result did not, however, reflect a statistically significant improvement. Most oncologists have now abandoned the use of chemotherapy by itself in the adjuvant setting.

In an effort to derive greater therapeutic benefit than can be achieved with either radiation therapy or chemotherapy alone, combinations of the two have been used in the adjuvant setting. In Intergroup Trial 0116, 556 patients who had undergone R0 resection of adenocarcinoma of the stomach or the esophagogastric junction were randomly assigned to treatment with either surgery alone or surgery plus postoperative chemoradiotherapy. Patients with tumors ranging from stage IB to stage IVM0 were included; the majority had T3 tumors and node-positive disease. The therapeutic regimen consisted of 5-FU and leucovorin administered concomitantly with 45 Gy of external-beam irradiation over a period of 5 weeks. Median overall survival in the surgery-only group was 27 months, compared with 36 months in the surgery-chemoradiation group. In addition, the 3-year survival rate was 41% in the
surgery-only group, compared with 50% in the surgery-chemoradia-
tion group. The hazard ratio for death in the surgery-only group as compared with the surgery-chemoradiation group was 1.35.

In the United States, the results of Intergroup Trial 0116 have led to the acceptance of chemoradiotherapy as standard adjuvant therapy for patients who have undergone curative-intent resection of gastric cancer. Nonetheless, numerous criticisms of this trial have been expressed. Specifically, a review of the operative and pathology reports of 453 of the patients revealed a lack of surgical standardization. When the extent of lymphadenectomy was categorized, the majority (54.2%) of the patients were found to have undergone a D0 dissection; 38.1% underwent a D1 dissection, and only 7.5% underwent a D2 or D3 dissection. These findings suggest that the main effect of the chemoradiation therapy may have been simply to compensate for inadequate surgery. This suggestion is supported by the observation that the number of patients with local and regional recurrences was higher in the surgery-only group (178 versus 101), whereas the number of patients with distant failure was slightly higher in the adjuvant-therapy arm (40 versus 32). Furthermore, when the Maruyama Index of Un-
resected Disease (a computer model developed for accurate pre-
diction of nodal station involvement in gastric cancer) was applied to the 556 patients eligible for the Intergroup Trial, the median Maruyama Index was 70. This value was far above the level considered to represent optimal surgical therapy (i.e., Maruyama Index < 5) and led the authors to conclude that the vast majority of patients in the trial had been surgically undertreated. Currently, physicians, especially in Europe, generally eschew adjuvant therapy after R0 resection of gastric cancer, except under the auspices of a clinical trial. The Radiation Therapy Oncology Group has initiated a phase II trial of adjuvant chemoradiotherapy using 45 Gy of external beam radiation with cisplatin and pax-
taxel, with or without 5-FU. If promising results are found, a phase III trial will follow. It is to be hoped that ongoing trials will shed further light on this complex management issue.

Neoadjuvant therapy As a response to the disappointing results of adjuvant therapy and the inability of many patients to regain adequate performance status after radical gastric surgery, neoadjuvant therapy protocols have been proposed. The theoretical benefits of a neoadjuvant treatment strategy include treat-
ment-induced tumor downstaging, which may enhance resectabil-
ity, and early administration of systemic therapy, which allows almost all patients to receive and complete the prescribed treat-
ment. Furthermore, because treatment is administered when mea-
surable disease is present, response to therapy may be assessed and continued only in patients who are likely to benefit. Finally, patients who are found to have rapidly progressive disease during preoper-
ative chemotherapy may be spared having to undergo a nonthera-
pic gastrectomy.

In a report of three phase II trials from the M. D. Anderson Cancer Center, encompassing 83 patients who received neoadjuvant chemotherapy before planned surgical resection, clinical response rates ranged from 24% to 38%, with three patients (4%) exhibiting a complete pathologic response. Sixty-one patients (73%) were able to undergo a curative-intent resection, and the response to chemotherapy was the only significant predictor of survival on multivariate analysis.

Preoperative chemoradiation therapy has also been shown to be feasible in phase II trials. In a 2001 trial that included 23 patients, 96% of the study population received combined-modality therapy. Nineteen patients (83%) were able to undergo sur-
gical resection with D2 lymphadenectomy; four patients (17%) had progressive disease and did not undergo resection. Morbidity and death rates were acceptable (32% and 5%, respectively), and 11% of patients exhibited complete pathologic responses. Overall, 63% of patients showed pathologic evidence of a signif-
icient treatment effect.

Newer neoadjuvant treatment strategies employ multiagent in-
duction chemotherapy followed by chemoradiotherapy and planned gastric resection in patients with locally advanced but potentially resectable gastric cancer.

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. Furth-
more, 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 evaluation have documented recurrent disease at the anastomosis, in the retroperito-
toneum, 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 pa-
ients 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 examina-
tions. Currently, the NCCN recommends that a complete history and physical examination be conducted every 4 months for 1 year, then every 6 months for 1 year, and then yearly thereafter. A complete blood count, serum electrolyte concentrations, and liver function studies should also be considered. Imaging studies (e.g., CT and endoscopy) are ordered as indicated, usually in response to new symptoms. In addition, long-term vitamin B12 supplementation should be initiated for patients who have under-
gone a proximal or subtotal gastrectomy.

Other 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 type. The stomach is the most common site of extranodal involve-
ment of non-Hodgkin lymphoma (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 ap-
petite, weight loss, vomiting, and bleeding. Overt clinical symp-
toms (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.76

**Investigative Studies**

The diagnosis of gastric lymphoma is most frequently established by means of endoscopy with biopsy. Staging studies include a comprehensive blood count, a lactate dehydrogenase (LDH) level, and a comprehensive chemistry panel; CT of the chest, the abdomen, and the pelvis; and, often, a bone marrow biopsy. All pathology slides should be reviewed by an experienced hematopathologist.77

**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.76 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).78

**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).79 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.80 Approximately 45% of all gastric lymphomas are low-grade mucosa-associated lymphoid tissue (MALT) lymphomas.75 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.81

**Nonsurgical therapy** Low-grade MALT lymphoma usually presents as stage I or II disease and has an indolent course. Since 1993, when regression of low-grade MALT lymphoma after eradication of *H. pylori* was first reported, numerous trials have documented the efficacy of anti-*H. pylori* therapy, with complete remission rates ranging from 50% to 100%.79 In the German MALT Lymphoma Study, the complete remission rate was 81%; 9% of patients exhibited partial responses, and 10% showed no response.82 Low-grade lymphomas that are more advanced or do not regress with antibiotic therapy may be treated with *H. pylori* eradication and radiation (with or without chemotherapy).83 For localized persistent disease, modest doses of radiation, on the order of 30 Gy, may be employed. When chemotherapy is required, multigent regimens, such as cyclophosphamide-vincristine-prednisolone (COP), are often used.

Approximately 55% of gastric lymphomas are high-grade lesions, which can occur with or without a low-grade MALT component.75 These lymphomas are treated with chemotherapy and radiation therapy according to the extent of the disease. The cyclophosphamide-doxorubicin-vincristine-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.84

**Surgical therapy** Surgical resection, once thought to be essential for the diagnosis, staging, and treatment of early-stage gastric lymphoma, now is 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.77 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 there was only one hemorrhage (in a patient treated with chemotherapy alone). Similarly, in a single-institution, prospective, randomized trial comparing chemotherapy alone with chemotherapy plus surgery for stage I and II lymphoma, there were no instances of perforation and only three instances of GI bleeding in the chemotherapy group, compared with two bleeding episodes in the surgery plus chemotherapy group.79

Currently, patients with early-stage high-grade gastric lymphomas are treated primarily with chemotherapy or radiation therapy; only rarely do they require surgical intervention for complications encountered during therapy. Patients with locally advanced (stage III) or disseminated (stage IV) gastric lymphoma are clearly best treated with chemotherapy, with or without radiation. Occasionally, surgery is indicated in such patients to treat residual disease confined to the stomach or to palliate bleeding or obstruction that does not resolve with nonoperative therapy. Primary surgical therapy is to be avoided in these patients because of the significant risk of complications and the delay in initiating systemic therapy.

**GASTROINTESTINAL STROMAL TUMOR**

Gastrointestinal stromal tumor (GIST), though relatively rare in absolute terms, is the most common sarcoma of the GI tract,85 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 cases86; 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.87 Thus, extended gastric resection, often including contiguous organs, was advised. Recurrence developed after R0 resection in approximately 50% of cases.88 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 the interstitial cell of Cajal, an intestinal pacemaker cell.89 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.86 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 of incidence is 63 years, and tumors are generally between 0.5 and 44 cm in diameter at the time of diagnosis (median diameter, 6 cm).86 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.
GASTRIC CARCINOID

Gastric carcinoid tumors are rare, accounting for fewer than 11% to 30% of all GI carcinoids and fewer than 1% of all gastric tumors. The median age at diagnosis is 62, and tumors are equally distributed between men and women.

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 polyoid. 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 (MEN I) and, like type I tumors, are usually small and multiple. They also grow slowly, but they 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%).

Table 4 American Joint Committee of Cancer TNM Clinical Classification of Small Bowel Carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary site</th>
<th>Regional lymph nodes</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>NX Regional lymph node(s) cannot be assessed</td>
<td>MX Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>N0 No regional lymph node metastasis</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa</td>
<td>N1 Regional lymph node metastasis</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor penetrates &lt; 2 cm into subserosa or into nonperitonealized perimural tissue (mesentry for jejunum or ileum, retroperitoneum for duodenum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor penetrates visceral peritoneum or directly invades &gt; 2 cm into adjacent structures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management

For patients with small, solitary type I tumors, endoscopic polypectomy [see 5:18 Gastrointestinal Endoscopy] or open resection via gastrotomy (local excision) [see 5:20 Gastric and Duodenal Dis.] is the procedure of choice. For patients with multiple or recurrent tumors, antrectomy [see 5:20 Gastric and Duodenal Dis.] is indicated to remove the source of the hypergastrinemia. 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, only a few thousand new cases of small bowel cancer are reported each year.95 The majority of small bowel malignancies are adenocarcinomas, lymphomas, or carcinoid tumors,96 though GISTs are being noted with increasing frequency in the small intestine. Treatment of lymphomas, carcinoid tumors, and GISTs in the small bowel is nearly identical to treatment of the same lesions in the stomach [see Other Gastric Malignancies, above] and thus will not be covered further in this chapter. Our focus here is on the presentation, diagnosis, and treatment of adenocarcinoma of the small bowel. Like gastric adenocarcinoma, small bowel adenocarcinoma is usually staged according to the AJCC/UICC TNM classification system [see Tables 4 and 5].

CLINICAL EVALUATION

Between 46% and 55% of small bowel adenocarcinomas occur in the duodenum.96,97 Patients frequently present with nausea, vomiting, abdominal pain, weight loss, and GI bleeding98; 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.97

INVESTIGATIVE STUDIES

When an adenocarcinoma is located in the duodenum, the diagnosis is often made by means of esophagogastroduodenoscopy (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 enteroscopy to be superior to the more commonly used small bowel follow-through in this setting, in that enteroscopy is better able to demonstrate fine mucosal detail.99 In experienced hands, enteroscopy may therefore be more sensitive.100 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 promising new method for the identification of small bowel tumors is wireless capsule endoscopy.101 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.102 For peripillary lesions, pancreaticoduodenectomy is typically required to achieve a margin-negative resection. For lesions in the distal duodenum, a segmental sleeve resection with a duodenojejunostomy 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.98

Because the presenting signs and symptoms are often vague and nonspecific, diagnosis is often delayed. In one series, only 6 (11%) of the 53 patients were suspected of having a small bowel tumor at admission.102 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.98

The 5-year survival rate continues to be low (24% to 37%).98,103,104 Significant predictors of good overall survival include complete (R0) resection and low AJCC tumor stage.98,103,104 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.103

References

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