A 29-Year Old Woman Presenting With Abdominal Pain and Vomiting

Bryan DiBuono, MD; William A. Ferrante, MD; Thomas Weed, MD; Ruben D. Vargas, MD; Jane K. Dry, MD; Claremont F. Carter, MD; and Fred A. Lopez, MD (Section Editor)

CASE PRESENTATION

A 29-year-old woman with no significant past medical history presented as an outpatient to her gynecologist for lower abdominal discomfort, which had been worsening for three months. The patient stated that the pain was of a dull, aching quality, had occurred daily, and was exacerbated by meals. She also stated that she had experienced a few episodes of non-bloody, non-bilious emesis over the preceding two weeks, and that she was not able to eat much over the same period because of feelings of fullness and bloating. She experienced a 10-pound unintentional weight loss over the preceding month. She admitted to occasional subjective fevers, nausea, vomiting, and generalized fatigue. She denied any headaches, chills, dysphagia, heartburn, chest pain, shortness of breath, change in bowel habits, or gastrointestinal bleeding.

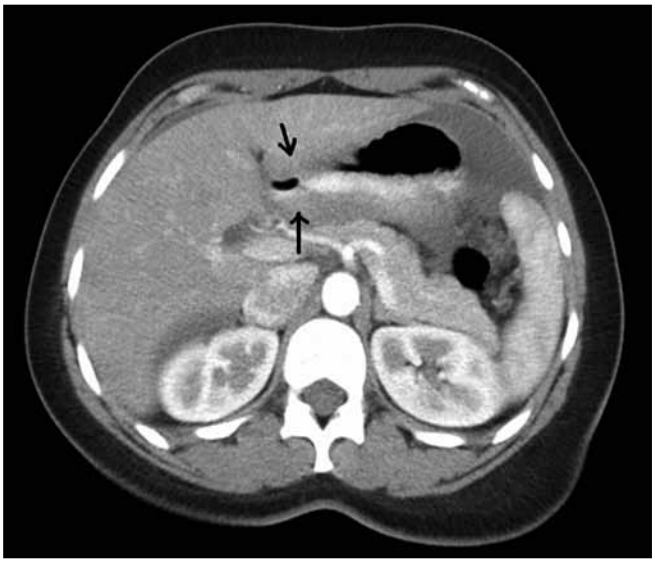

Figure 1. A computed tomographic (CT) scan of the abdomen showing thickening of the gastric antrum (arrows).

The patient underwent a remote laparoscopic cholecystectomy secondary to gallstones, but denied any other significant past medical problems. Her mother died of gastric carcinoma at 46 years of age. She denied any history of tobacco or illicit drug use, and admitted to only occasional alcohol use. She lives with her husband and two children, has no primary care physician, no known medication allergies, and is on no medications as an outpatient. A computed tomographic (CT) scan of the abdomen and pelvis revealed thickening of the gastric antrum, as well as a small amount of ascites in the pelvis (Figure 1). The patient was then referred for endoscopic evaluation of her stomach.

Vital signs at the time of the patient's presentation for endoscopy included a temperature of 99.2°F, a pulse of 105 beats per minute, respiratory rate of 18 breaths per minute, blood pressure of 132/78 mm Hg, oxygen saturation of 98% on room air, and a weight of approximately 70.0 kg. The patient was alert, oriented, and in no apparent distress. Her pupils were equally round and reactive, and her sclerae were anicteric. Her neck was supple with no masses or elevation in her jugular venous pressure, and her oropharynx was clear. On cardiovascular exam, she was tachycardic with no appreciable murmur and a normal point of maximal impulse. Her lungs were clear to auscultation bilaterally. Her abdomen was mildly protuberant, but soft with mild, diffuse tenderness to palpation and no shifting dullness or apparent fluid wave. Bowel sounds were normal. No cyanosis, clubbing, or edema of her extremities was

noted, and she had strong palpable peripheral pulses. Her neurologic exam was grossly unremarkable, with normal cranial nerve function, normal strength and sensation in all extremities, and appropriate deep tendon reflexes bilaterally.

Serum chemistry drawn prior to endoscopic examination revealed a sodium of 141 mmol/L (normal range, 135-146 mmol/L), potassium of 3.6 mmol/L (normal range, 3.6-5.2 mmol/L), chloride of 104 mmol/L (normal range, 96-110 mmol/L), bicarbonate of 25 mmol/L (normal range, 24-32 mmol/L), blood urea nitrogen of 8 mg/dL (normal range, 7-25 mg/dL), creatinine of 0.58 mg/dL (normal range, 0.50-1.10 mg/dL), glucose of 81 mg/dL (normal range, 65-99 mg/dL), and calcium of 10.0 mg/dL (normal range, 8.4-10.3 mg/dL). A liver function profile revealed a total protein of 8.8 gm/dL (normal range, 6.0-8.0 gm/dL), albumin of 4.7 gm/dL (normal range, 3.4-5.0 gm/dL), total bilirubin of 0.7 mg/dL (normal range, <1.3 mg/dL), AST of 36 U/L (normal range, <45 U/L), ALT of 25 U/L (normal range, <46 U/L), and alkaline phosphatase of 58 U/L (normal range, 20-120 U/L). Coagulation studies revealed a protime of 13.2 sec (normal range, 10.0-13.2 sec), an INR of 1.1 (normal range, 0.9-1.1), and a prothrombin time of 32.1 sec (normal range, 24.0-38.0 sec). The patient's blood count revealed a white blood cell count of 5.8 x 10^3/uL (normal range, 4.5-11.0 x 10^3/uL), with a differential of 68% neutrophils, 23% lymphocytes, 7% monocytes, and 2% eosinophils; hemoglobin of 13.2 gm/dL (normal range, 12.0-16.0 gm/dL), hematocrit of 39.3% (normal range, 35%-46%), platelet count of 268 x 10^3/uL (normal range, 130-400 x 10^3/uL), mean corpuscular volume of 89.0 FL (normal range, 80-100 FL), and red cell distribution width of 13.4% (normal range, 11.5%-14.5%).

Esophagogastroduodenoscopy (EGD) was performed which revealed a normal esophagus and duodenum; however, the gastric mucosa was remarkable for panatrophic gastritis and a large, heaped mass with central ulceration and adherent clot extending from the mid body of the stomach, along the posterior lesser curvature, to the prepyloric antrum (Figures 2, 3, and 4). The mass appeared diffusely hypervascular and resulted in antral deformity which was felt to be causing partial obstruction of the gastric outlet. Multiple biopsies were taken of the area. The samples were noted to be negative for the presence of *Helicobacter pylori*. Histologic examination of the samples revealed diffuse, poorly differentiated, infiltrating gastric adenocarcinoma with a signet ring cell pattern (Figures 5 and 6). The tumor was subsequently found on immunohistochemical analysis to be negative for expression of the human epidermal growth factor receptor 2 (HER2) protein.

The patient re-presented to the hospital one day after her EGD because of abdominal discomfort and intractable nausea and vomiting. She was treated symptomatically with nasogastric (NG) tube suction, promethazine, and ondansetron. She was also given hydromorphone as needed for pain. General surgery and hematology/oncology were consulted. A central catheter was placed for administration of chemotherapy and she was discharged home with plans for follow-up evaluation in surgery clinic. The patient, however, presented again five days later with nausea, vomiting, and abdominal pain. Once stable, the patient was taken to the operating room for exploratory laparotomy, at which time six liters of ascitic fluid were removed and diffuse involvement of the small bowel, large bowel, and mesentery with multiple tumor foci were noted. The primary mass was noted to be fixed to the retroperitoneum and was not resectable; therefore, a palliative gastrojejunostomy was performed. The patient's hospital course was complicated

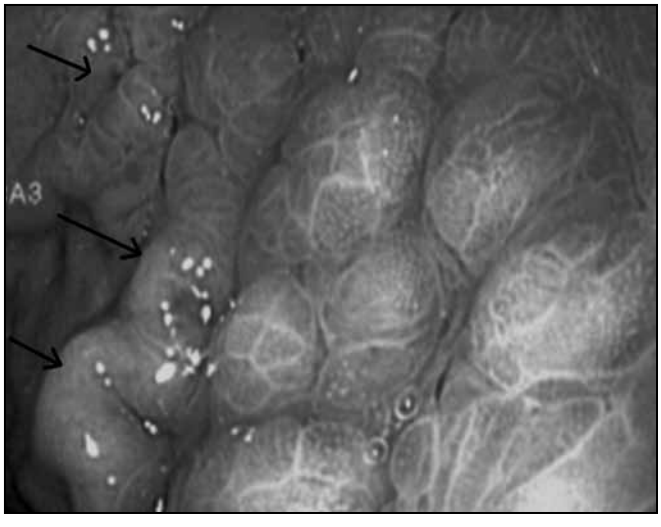

Figure 2. An endoscopic photograph of the gastric mucosa with arrows showing the interface between normal gastric mucosa and a large heaped mucosal mass.

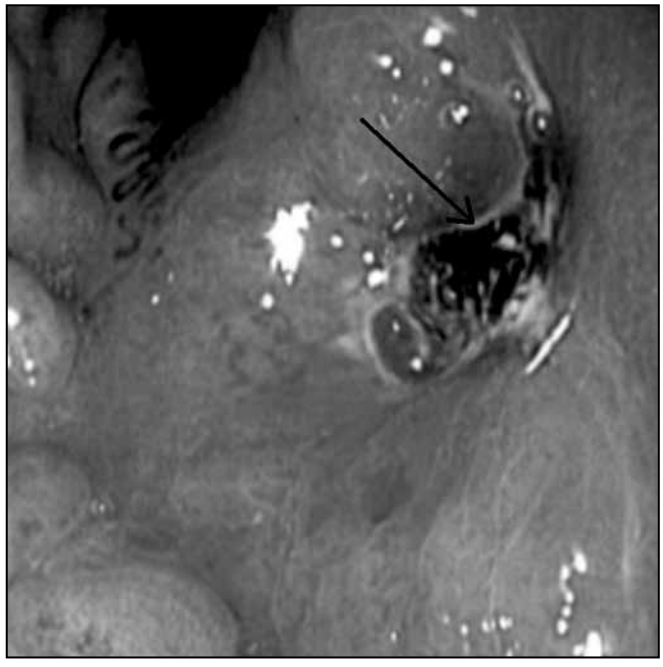

Figure 3. An endoscopic photograph of the gastric mass showing central ulceration with overlying clot (arrow).

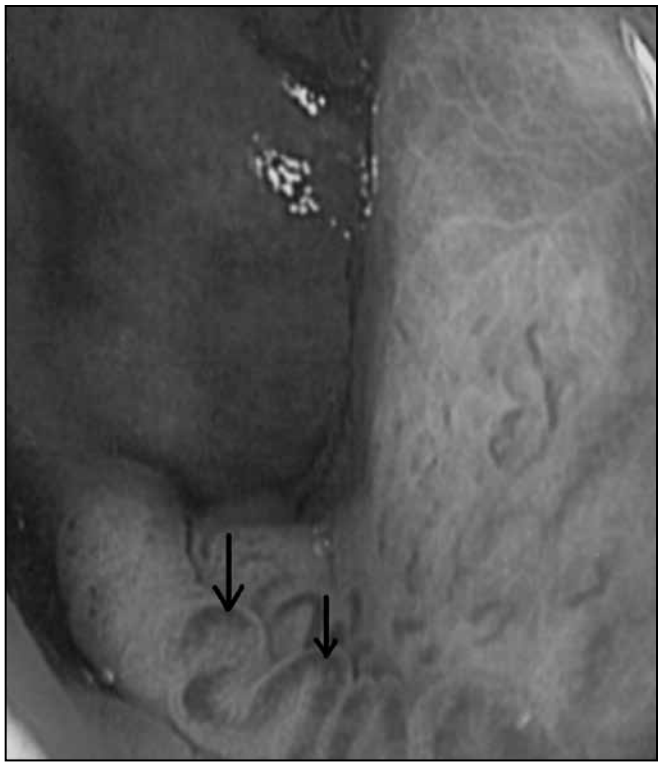

Figure 4. An endoscopic photograph showing hypervascular markings (arrows) of the gastric mass.

by hospital-acquired pneumonia, which was treated with antibiotics. She was eventually discharged to home with plans to receive palliative chemotherapy consisting of cisplatin and irinotecan.

DISCUSSION

Gastric cancer is a common form of cancer worldwide, with a variety of factors contributing to its epidemiologic distribution, including geography, ethnicity, and socioeconomic status. It has been estimated that its annual incidence represents 9.9% of all new cancers, accounting for approximately 870,000 cases per year, with a mortality of approximately 650,000 per year.[1] Until it was overtaken by lung cancer in the 1980s, gastric cancer was the leading cause of cancer death worldwide. Currently, it is second to lung cancer, accounting for 10.4% of cancer deaths worldwide.[2] There has been a notable decline in incidence in recent years which may be attributed, in part, to early identification of risk factors and technological advances in food preservation. The highest incidences of gastric cancer are noted in populations of Eastern Asia, Eastern Europe, and South America, while North America and Northern Europe currently have lower rates of incidence.

There are two types of gastric cancer currently identified, namely the so-called intestinal type and the diffuse, infiltrative type. The intestinal type, which has been on the decline, exhibits a male predilection, presents in older age at time of diagnosis, and is increasingly linked to identifiable environmental, genetic, and lifestyle-associated risk factors.[3] The diffuse, or infiltrative, type exhibits no gender predominance, occurs in younger individuals, and usually portends a worse prognosis. It has also been found that the incidence of tumors arising in the distal portion of the stomach has been steadily declining, while those occurring more proximally, particularly in the gastric cardia, have been increasing in incidence.[4] These proximal tumors are more aggressive, and seem to share some features with esophageal cancer which has led to changes in staging systems of gastric cancer based on location.

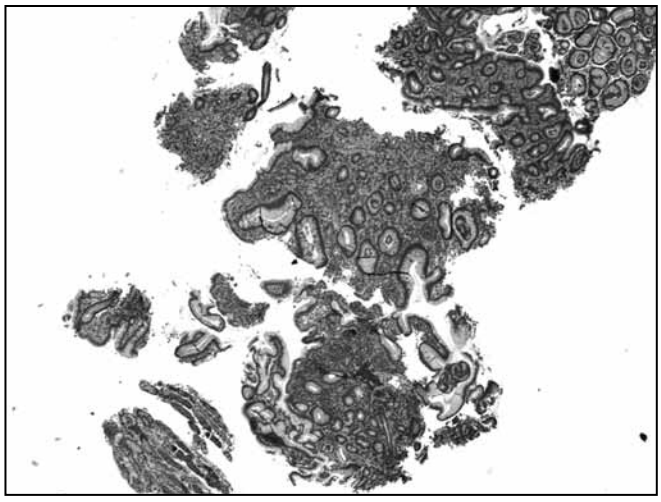

Figure 5. A low-power photomicrograph showing invasive infiltrate disrupting the architecture of the gastric mucosa.

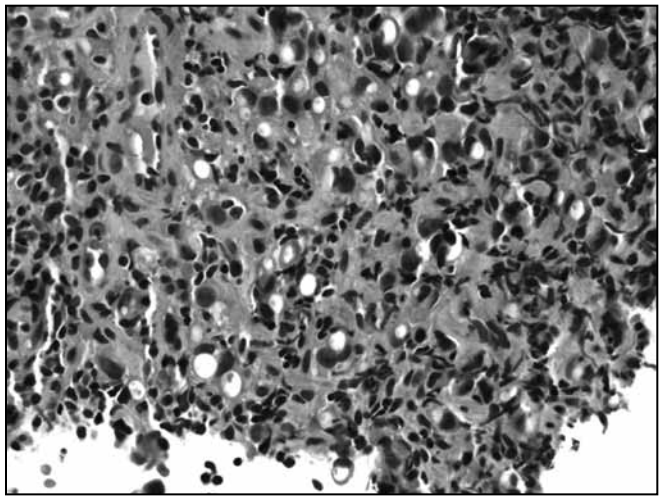

Figure 6. A high-power photomicrograph showing poorly differentiated adenocarcinoma of the stomach with signet ring cells.

CLINICAL PRESENTATION

The majority of patients diagnosed with gastric cancer are symptomatic, because most have advanced disease at the

time of presentation. These patients have extensive disease that is usually not amenable to surgical care. Patients who have potentially curable disease usually have early cancers detected on screening endoscopy, although such screening protocols only exist in endemic areas.

The most common presenting symptoms are weight loss and abdominal pain, which is usually epigastric and vague early in the course of the disease.[5] Other possible presentations include nausea and early satiety, which may be secondary to mass effect of the tumor or poor distensibility of the stomach resulting from infiltrative disease (linitis plastica). Proximal tumors may cause dysphagia or pseudoachalasia, while distal tumors may result in symptoms of gastric outlet obstruction. At least 25% of patients diagnosed with gastric cancer have a history of gastric ulcers, a finding which underscores the need to follow gastric ulcers to healing and consider further workup or resection if healing does not occur.[8] Other presentations may be due to tumor spreading, such as feculent vomiting resulting from a gastrocolic fistula or ascites from peritoneal carcinomatosis.

Metastasis may occur to several sites, with the liver, peritoneum, and lymph nodes being more common than other areas such as the ovaries (Krukenberg tumor), bones, and central nervous system. Liver metastases may manifest in laboratory workup with elevated alkaline phosphatase in the absence of clinical liver disease. Lymphatic metastases of gastric cancer may be found in the supraclavicular (Virchow's node), axillary (Irish node), or periumbilical (Sister Mary Joseph's node) areas.[5]

Paraneoplastic syndromes may also result from gastric cancer. These include diffuse seborrheic keratoses (sign of Leser-Trelat), acanthosis nigricans (dark, velvety patches on the skin), microangiopathic hemolytic anemia, membranous nephropathy, hypercoaguability (Trousseau's syndrome), and polyarteritis nodosa.[5]

PATHOGENESIS

The two types of gastric cancer, namely the intestinal type and the diffuse infiltrative type, differ in terms of their pathogenesis.[4] Both may be associated with *H. pylori* infection, although this association is not strongly observed in the diffuse type.

The intestinal type, which is the most common type, exhibits a stepwise progression through several stages.[7] *H. pylori* infection leads to chronic active gastritis. Progression to atrophic gastritis may then occur, which involves a relative loss of mucus-producing cells in the gastric antrum, as well as parietal and chief cells in the corpus. This, in turn, results in decreased acid production, increased luminal pH, decreased absorption of the antioxidant vitamin C, and increased potential for cellular proliferation secondary to a rise in gastrin production. With the rise in gastric pH, colonization by bacteria which elaborate mutagenic compounds is enabled. The resulting cellular damage, increased production of reactive oxygen species, and increased cell turnover sets the stage for carcinogenesis. The subsequent appearance of tubular glands with an intestinal phenotype corresponds to a precancerous lesion called intestinal metaplasia (IM). This usually occurs first at the antrum-corpus junction and enlarges in area over time. These areas may resemble small intestinal mucosa (complete IM) with a brush border and regularly intervening goblet cells, or colonic mucosa (incomplete IM) characterized by irregular appearance of goblet cells. Hypochlorhydria, decreased secretion of normal gastric peptides, and possible early dysplasia, marked by cellular disorganization and large, hyperchromatic nuclei, may result from incomplete IM, and therefore closer surveillance for progression to carcinoma may be required in these cases.[8]

Theories to explain the carcinogenic potential of *H. pylori* include induction of mutagenic nitric oxide synthase by inflammatory cells responding to infection, and sequential accumulation of genetic abnormalities over time, including those involving oncongenes or tumor suppressor genes, namely K-ras, c-met, APC, p53, and others.[9] Most invasive carcinomas occur as ulcerated masses at the incisura angularis; however, more proximal lesions, which tend to be more aggressive, similar in behavior to esophageal cancers, and worse prognostically, can occur. Persons with lifelong *H. pylori* infection may take as long as 40 years to progress from the incipient stage to carcinoma.[7] There has been a recent decline in this type of gastric cancer with attempts at *H. pylori* eradication, and regression of premalignant lesions has been noted with treatment of *H. pylori*.[10]

Diffuse type gastric cancers usually exhibit a much more rapid clinical progression, poorer prognosis, and higher potential for metastasis than do intestinal type cancers. Infiltrative conditions, such as linitis plastica may result from this type, and histologic examination may reveal signet ring cells and no gland formation. The pathogenesis of this type is thought to involve defective intracellular adhesions due to a genetic loss of expression of the cellular protein E-cadherin (CDH1 gene).[11] This condition, called hereditary diffuse gastric cancer (HDGC), is inherited in an autosomal dominant fashion with penetrance varying from 40%-67% in males and from 60%-83% in females.[12] Because of this variable penetrance, some individuals may be silent carriers of the disease. In addition, there is no identified precancerous lesion as in the intestinal type, and the lesions may be multifocal and lying beneath an intact mucosal surface, thereby making diagnosis much more difficult.[13] Strong consideration must be given to family members of affected individuals with regard to genetic testing and possible prophylactic gastrectomy.

RISK FACTORS AND SCREENING

In intestinal type gastric cancers, there are a variety of potential risk factors that have been identified which may

lead to chronic atrophic gastritis, including pernicious anemia, high dietary salt intake, and *H. pylori* infection. Gastric resection as a component of bariatric surgery, which results in increased reflux of alkaline bile into the gastric lumen, may also lead to increased pH and bacterial colonization.[14] Many of these risk factors are reversible, and the precancerous lesion, IM, has been demonstrated to regress with the removal of some of these risk factors. Overall, an increase in cellular proliferation and luminal mutagens, along with a decrease in luminal protective factors provide a favorable environment for the development of gastric cancer.

Environmental risk factors that may potentially contribute to carcinogenesis are also abundant. Dietary factors associated with increased risk include high intake of nitrates, as in fried and processed foods, decreased intake of antioxidants via fresh vegetables and citrus fruits, and high intake of salt, which can lead to mucosal disruption.[15] Potentially reversible risk factors such as morbid obesity, cigarette smoking, and lower socioeconomic status have also been identified.[16,17]

Host factors that may confer higher risk for the development of cancer include mutation of the E-cadherin gene (as in the diffuse type),[11] genetic associations with certain ABO blood groups, male gender, and familial cancer syndromes such as hereditary diffuse gastric cancer (HDGC), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, and hereditary non-polyposis colorectal cancer (HNPCC), but consideration of these entities is beyond the scope of this discussion. Hypertrophic gastropathy (Menetrier's disease) and several immunodeficiency syndromes have also been linked with gastric cancer, but the strength of these associations is uncertain.

The utility and cost-effectiveness of screening programs for gastric cancer remain the subjects of much debate, and such programs are currently only in place in endemic areas such as East Asia and parts of South America.[24] The methods vary, but most employ a risk interview and barium studies. Some serologic markers, including serum pepsinogen, are currently used, and endoscopy is reserved for those with increased risk. For persons with two or more cases of diffuse type gastric cancer in first and second degree relatives with one occuring before 50 years of age, or three or more cases occurring at any age, genetic testing for the CDH1 mutation is recommended, along with serial endoscopy with multiple biopsies. Those patients who are found to have the CDH1 mutation on genetic testing should be considered for prophylactic gastrectomy after age 20, but patients may also opt for a vigorous surveillance endoscopy schedule in order to avoid surgery.[19] Currently, there are no recommendations for mass screening in the United States.

DIAGNOSIS AND STAGING

Once a detailed history, physical, and laboratory evaluation reveals a clinical suspicion for gastric cancer, timely diagnostic evaluation should be performed. The procedure of choice is endoscopic evaluation with direct visualization of the gastric mucosa. Any suspicious lesion discovered during EGD should be biopsied, as up to 5% of malignant lesions and ulcers appear grossly benign. Diagnostic yield is increased with the number of biopsies obtained, with the sensitivity for a single biopsy being approximately 70%, while sensitivity after performing seven or more biopsies is increased to 98%.[20] For diffusely infiltrating carcinomas, diagnosis may be more difficult as the lesions may be submucosal and biopsies may be too superficial. Diagnosis of this type of lesion may be aided by radiologic studies, as linitis plastica often has a classic appearance on barium swallow secondary to the resulting decrease in gastric distensibility. The need for follow-up endoscopy to document healing of biopsied gastric ulcers is controversial, but current recommendations are to repeat EGD after eight to 12 weeks to verify mucosal healing.[21] Barium studies are of limited use, as they may be falsely negative in up to 50% of cases.

Two major staging systems for gastric cancer currently exist. The Japanese staging system is elaborate and based mainly on anatomic location of the tumor and lymph node stations. The system developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is more commonly used, especially in the Western Hemisphere, and is based on tumor (T), node (N), and metastasis (M) stages.[22] Tumor stage is related to

the depth of invasion, while nodal stage is based upon the number of positive lymph nodes, and metastasis stage is based on the presence or absence of metastases. T0 refers to absence of evidence of primary tumor, while Tis refers to carcinoma in situ. T1 lesions invade the lamina propria, muscularis mucosa, and/or submucosa, T2 lesions invade the muscularis propria, and T3 lesions invade subserosal tissue without involvement of the visceral peritoneum or adjacent structures. T4a lesions invade the serosa and T4b lesions invade adjacent organs. Nodal stage has been recently updated, with N1 corresponding to one to two positive nodes, N2 corresponding to three to six positive nodes, and N3 corresponding to greater than or equal to seven positive nodes. M stage is designated to be either zero or one depending on the presence or absence of metastases.[22]

Using the above designations to stage gastric cancer anatomically, Stage 0 disease is defined as carcinoma in situ with no nodal metastases. Stage I disease refers to T1 lesions with an N stage of zero or one, or T2N0 lesions. Stage II disease encompasses those T1 lesions with N2 or 3 stages, T2 lesions with N1-N2, T3 lesions with N stage less than or equal to one, and T4a lesions with an N stage of zero. Stage III disease refers to all other T4 lesions, T3 lesions with N scores of two or more, or T2N3 lesions. Stage IV disease refers to any lesion with distant metastasis (M1). Recent changes in staging schemes have resulted in tumors arising at the esophagogastric junction (EGJ), or in the cardia of the stomach within 5 cm of the EGJ being staged as esophageal rather than gastric cancers, a system which is more complex. In addition, the T categories were altered to correspond to those of cancers of the esophagus and the bowel, while positive peritoneal cytology has been designated as M1.[22]

Initially, clinical staging and preoperative evaluation, which can help identify patients likely to be curable versus those with systemic disease, is performed, although staging is most accurately defined through surgical evaluation. One useful tool in this area is abdominopelvic CT. If this modality detects visceral metastases, surgery may be avoided. The limitation, however, is false negativity, in that 20%-30% of those with negative CT scans will have metastases noted during exploratory laparotomy. In addition, CT scan accurately assesses depth of invasion only 50%-70% of the time.[23] Endoscopic ultrasound (EUS) is the most reliable nonsurgical method for assessing depth of invasion and possesses the capacity for fine needle aspiration of lesions. However, this modality is operator dependent, only slightly better than a CT scan for assessing N stage, and is costly. Although helpful in patients with early gastric cancer, EUS is not universally recommended for preoperative staging of all patients with gastric cancer. Positron emission tomography (PET) may be integrated with CT to confirm malignant lymph nodes, and is more sensitive than a CT scan for distant metastases. However, a PET scan, which is based on metabolic activity of cancer cells, is not helpful if negative because tumor cells may have decreased metabolic activity and show little to no uptake. PET scans, therefore, usually do not impact the decision to proceed to surgery.[24] Serologic markers, such as carcinoembryonic antigen (CEA) and the glycoprotein antigens CA 19-9, CA 125, and CA 72-4 may be elevated in gastric cancer, but are not especially sensitive or specific, and are thus not used as diagnostic tests.[25]

Surgical staging offers the advantage of direct visualization of the abdominal viscera, and provides the opportunity to perform peritoneal cytology. Indeed, 20%-30% of those with T stages greater than one will have peritoneal involvement despite negative findings on CT scanning. Staging laparoscopy may therefore be used in patients with T stages greater than one, no histologic evidence of distant disease, and who do not otherwise require palliative gastrojejunostomy.[26]

TREATMENT

Following staging, one can then proceed with treatment. For localized disease, the goal is complete eradication of the tumor with dissection of adjacent lymph nodes. This approach offers the best chance for cure, as well as symptom palliation, and is the preferred strategy unless there is evidence of disseminated disease, neoadjuvant chemotherapy is recommended, or there are other contraindications to surgery. For mucosal and submucosal lesions, endoscopic mucosal resection (EMR) is emerging as a treatment option, but is currently performed by relatively few endoscopists in the United States. Contraindications to EMR include depressed lesions, failure of the lesion to lift with submucosal saline injection, and deep invasion. Further consideration of EMR is beyond the scope of this discussion.

For lesions in the proximal one-third of the stomach, total gastrectomy is the preferred procedure, while tumors

of the lower two-thirds may be treated with subtotal gastrectomy with lymph node dissection.[27] Exceptions may be made in the case of large mid-gastric tumors, which may require total gastrectomy, even though they are not truly proximal tumors. Most studies show that post-operative quality of life is better following subtotal versus total gastrectomy; long term data, however, is limited.[28]

For cancers of the esophago-gastric junction (EGJ), which are staged as esophageal cancers rather than gastric cancers, the decision is more complex. Depending on their exact location and extent, EGJ cancers may be treated with proximal subtotal gastrectomy with lymph node dissection, although total gastrectomy is still preferred by most surgeons due to increased risk of reflux esophagitis following proximal subtotal gastrectomy and possible failure to remove all involved lymph nodes.[28] Surgical techniques utilized for EGJ cancers vary according to the tumor characteristics, and may involve a total abdominal approach or a thoracoabdominal approach, depending on the proximal extent of the tumor.

Linitis plastica is usually extensively infiltrative, and may require wide excision and dissection of lymph nodes. Because of the complexity of the procedure, as well as the extremely poor prognosis associated with this disease, most surgeons consider the presence of linitis plastica to be a contraindication to surgery.

The use of chemotherapy, radiotherapy, or a combination of the two in adjuvant and neoadjuvant roles has been explored in an attempt to improve outcomes in patients with gastric cancer. While parts of Europe and Japan hold adjuvant chemotherapy alone or a combination of adjuvant and neoadjuvant chemotherapy as the standard of care for gastric cancer, the current standard in the United States is post-operative chemoradiotherapy. The regimen employed usually consists of monthly administrations of 5-fluorouracil (5-FU) and leucovorin in five day cycles, as well as 25 days of radiotherapy, with 5-FU and leucovorin on days one through four and 23-25, beginning one month after the first cycle of chemotherapy. For cancers of the EGJ, this regimen is also employed, but in a neoadjuvant role.[29] There is currently no defined role for intraperitoneal chemotherapy.

In some cases of patients with locally advanced but nonmetastatic disease who are initially unresectable, neoadjuvant chemotherapy or chemoradiotherapy is employed to potentially downstage tumors to make them more amenable to resection. Indeed some of these patients may be sufficiently downstaged that they may undergo potentially curative resection, however, this is an area which is currently still under study.[30]

For those with unresectable or metastatic disease, chemotherapy for palliation of symptoms and modest survival improvement is the mainstay of treatment. While chemotherapy may improve some symptoms such as malignant dysphagia, other symptoms such as pain, obstruction, or bleeding may require intervention from other disciplines such as surgery and endoscopy. There are currently many different chemotherapeutic agents, used either alone or in combination, which are currently employed in the treatment of unresectable gastric cancer. At present, there is no consensus on which constitutes the "first line" therapy, but it is generally agreed upon that combination therapy is superior to montherapy in terms of response, with no significant survival difference being observed.[31] Most regimens still employ therapy with cisplatin and 5-FU in combination with other agents, however, many alterations may be made to tailor the regimen to the patient. In some studies, irinotecan in combination with cisplatin, when compared to the standard cisplatin plus 5-FU regimen, has shown a nonsignificant trend toward improved survival, has been well tolerated, and is emerging as an attractive initial choice for many practitioners.[32]

Several biologic agents which target various cellular growth factor receptors, including HER2, EGFR, and VEGF, are being studied and are employed in selected cases of unresectable gastric cancer. In fact, it is currently recommended that affected patients be tested for overexpression of the receptor HER2 to help guide therapy. Approximately 25% of gastric cancers overexpress this receptor, and in these cases, trastuzumab, which is an anti-HER2 antibody approved for treatment of breast cancer, is recommended as an adjunct to chemotherapy.[33]

Therapeutic options for local palliation of symptoms such as nausea, pain, obstruction, and bleeding include palliative gastrectomy, surgical bypass via gastrojejunostomy, radiation therapy, and endoscopic stent placement. Before employing these methods, one must take into account the individual patient's prognosis in order to avoid excessive morbidity and inpatient hospital stays in those with limited life expectancies.

PROGNOSIS

Prognosis after surgical intervention for gastric carcinoma varies widely according to the extent of disease as defined by the stage. In general, better outcomes are observed in Asian populations than in Western populations. Five-year survival rates as recently observed in Western populations are 58%-78% for Stage I disease, 34% for Stage II, 8%-20% for Stage III disease, and approximately 7% for Stage IV.[34] Modest improvements have come about with the emergence of newer chemotherapeutic agents, but overall, much work remains to be done in this area.

Disease recurrence may present as local recurrence or distant metastasis, although distant failures are more common. Sites of local recurrence include the margins of resection and the regional nodal areas. Distant recurrence usually involves the liver and peritoneum. In general, curative resection of recurrent disease is not attempted, and most of these patients are offered chemotherapy for palliation.

REFERENCES

1. Lau M, Le A, El-Serag HB. Noncardia gastric adenocarcinoma remains an important and deadly cancer in the United States: secular trends in incidence and survival. *Am J Gastroenterol* 2006;101:2485-2492.
2. Stewart B, Kleihues P (editors). *World Cancer Report*. Lyon, France: IARC Press;2003:194-195.
3. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31-49.
4. Locke GR III, Talley NJ, Carpenter HA, et al. Changes in the site- and histology-specific incidence of gastric cancer during a 50-year period. *Gastroenterology* 1995;109:1750-1756.
5. Fuchs CS, Mayer RJ. Gastric carcinoma. *New Engl J Med* 1995;333:32-41.
6. Wanebo HJ, Kennedy BJ, Chmiel J, et al. Cancer of the stomach. A patient care study by the American College of Surgeons. *Ann Surg* 1993;218:583-592.
7. Correa P. Human gastric carcinogenesis: A multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992;52:6735-6740.
8. Filipe MI, Potet F, Bogomoletz WV, et al. Incomplete sulphomucin-secreting intestinal metaplasia for gastric cancer. Preliminary data from a prospective study from three centres. *Gut* 1985;26:1319-1326.
9. Smith MG, Hold GL, Tahara E, et al. Cellular and molecular aspects of gastric cancer. *World J Gastroenterol* 2006;12:2979-2990.
10. Mera R, Fontham ET, Bravo LE, et al. Long term follow up of patients treated for *Helicobacter pylori* infection. *Gut* 2005;54:1536-1540.
11. Graziano F, Humar B, Guilford P. The role of the E-cadherin gene (CDH1) in diffuse gastric cancer susceptibility: from the laboratory to clinical practice. *Ann Oncol* 2003;14:1705-1713.
12. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998;392:402-405.
13. Charlton A, Blair V, Shaw D, et al. Hereditary diffuse gastric cancer: predominance of multiple foci of signet ring cell carcinoma in distal stomach and transitional zone. *Gut* 2004;53:814-820.
14. Stalnikowicz R, Benbassat J. Risk of gastric cancer after gastric surgery for benign disorders. *Arch Intern Med* 1990;150:2022-2026.
15. Kono S, Hirohata T. Nutrition and Stomach Cancer. *Cancer Causes Control* 1996;7:41-55.
16. Yang P, Zhou Y, Chen B, et al. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer* 2009;45:2867-2873.
17. Tredaniel J, Boffetta P, Buiatti E, et al. Tobacco smoking and gastric cancer: review and meta analysis. *Int J Cancer* 1997;72:565-573.
18. Leung WK, Wu MS, Kakugawa Y, et al. Screening for Gastric Cancer in Asia: current evidence and practice. *Lancet Oncol* 2008;9:279-287.
19. Caldas C, Carneiro F, Lynch HT, et al. Familial gastric cancer: overview and guidelines for management. *J Med Genet* 1999;36:873-880.
20. Graham DY, Schwartz JT, Cain GD, et al. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. *Gastroenterology* 1982;82:228-231.
21. Pruitt R. Endoscopy, gastric ulcer, and gastric cancer. Follow-up endoscopy for all gastric ulcers? *Dig Dis Sci* 1993;38:284-288.
22. Edge SB, Byrd DR, Compton CC, et al (editors). *AJCC (American Joint Committee on Cancer) Cancer Staging Manual*, 7th ed. New York, NY: Springer; 2010:117.
23. Davies J, Chalmers AG, Sue-Ling HM, et al. Spiral computed tomography and operative staging of gastric carcinoma: a comparison with histopathological staging. *Gut* 1997;41:314-319.
24. Mukai K, Ishida Y, Okajima K, et al. Usefulness of preoperative FDG-PET for detection of gastric cancer. *Gastric Cancer* 2006;9:192-196.
25. Marrelli D, Pinto E, De Stefano A, et al. Clinical utility of CEA, CA19-9, and CA 72-4 in the follow-up of patients with resectable gastric cancer. *Am J Surg* 2001;181:16-19.
26. Sarela AI, Lefkowitz R, Brennan MF, et al. Selection of patients with gastric adenocarcinoma for laparoscopic staging. *Am J Surg* 2006;191:134-138.
27. Bozzetti F, Marubini E, Bonfanti G, et al. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. *Ann Surg* 1999;230:170-178.
28. Tyrvainen T, Sand J, Sintonen H, et al. Quality of life in the long-term surviviors after total gastrectomy for gastric carcinoma. *J Surg Oncol* 2008;97:121-124.
29. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-730.
30. Ajani JA, Mansfield PF, Janjan N, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol* 2004;22:2774-2780.
31. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006;24:2903-2909.
32. Ajani JA, Baker J, Pisters PW, et al. CPT-11 plus cisplatin in patients with advanced untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer* 2002;94:641-646.
33. Tanizaki J, Okamoto I, Takezawa K, et al. Synergystic antitumor effect of S-1 and HER2-targeting agents in gastric cancer with HER2 amplification. *Mol Cancer Ther* 2010;9:1198-1207.
34. Hundahl SA, Phillips JL, Menck HR. The National cancer data base report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. *Cancer* 2000;88:921-932.

Dr. DiBuono is a postdoctoral fellow in gastroenterology in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans. **Dr. Ferrante** is the program director of the gastroenterology fellowship in the Department of Internal Medicine, Section of Gastroenterology at Louisiana State University Health Sciences Center in New Orleans. **Dr. Weed** is chief of surgery at Leonard J. Chabert Medical Center in Houma, Louisiana. **Dr. Vargas** is a staff hematologist/oncologist at Leonard J. Chabert Medical Center in Houma, Louisiana. **Dr. Dry** is a staff pathologist at Leonard J. Chabert Medical Center in Houma, Louisiana. **Dr. Carter** is a staff radiologist at Leonard J. Chabert Medical Center in Houma, Louisiana. **Dr. Lopez** is the Richard Vial Professor and vice chair for education in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans.