Gastric Adenocarcinoma: Part Two

DIAGNOSIS AND STAGING

Clinical Manifestations

Early gastric cancer is detected commonly in Japan where there is an aggressive screening program. Unfortunately, in the United States, most gastric cancers present at an advanced stage. This is because screening programs are not employed in the United States, and patients are usually diagnosed once symptoms are investigated. Symptoms generally do not occur until the cancer has invaded the muscularis propria or metastasized to distant organs. Weight loss and persistent abdominal pain are the most common symptoms, occurring in greater than 60% and 50% of patients, respectively (1). Location may determine symptom presentation, with antral cancers commonly presenting with gastric outlet obstruction and cardia cancers presenting with dysphagia. Pseudoachalasia can occur with tumor involvement of Auerbach’s plexus. Feculent emesis or passage of recently ingested food per rectum can be seen with a gastrocolic fistula.

Physical examination is usually unremarkable and nonspecific. Rarely an epigastric mass, hepatomegaly, ascites, or lower extremity edema is present. When there are physical findings, the most common are cachexia and evidence of bowel obstruction. Metastatic disease may manifest as a palpable lymph node at the umbilicus (Sister Mary Joseph node) or supraclavicular region (Virchow’s node). Metastasis to the ovaries (Krukenberg’s tumor) or rectal shelf can occur, occasionally translating into a palpable mass. Paraneoplastic phenomena are unusual and include thrombophlebitis or Trousseau’s syndrome, acanthosis nigricans, and seborrheic keratoses or Leser-Trelat sign, although none are specific for gastric cancer.

DIAGNOSIS

Upper Endoscopy

Physical examination and blood work are nonspecific, and there are no reliable tumor markers for gastric cancer. Upper endoscopy with tissue acquisition is the diagnostic procedure of choice (Figure 1a). The reported sensitivity of upper endoscopy ranges from 80%–99% (2,3). However, it was determined many
years ago that increasing the number of biopsies from the edge of a non-healing gastric ulcer increases the sensitivity (4). Newer techniques are being examined to increase the sensitivity for diagnosing early gastric cancer and to better delineate pre-cancerous changes within the stomach. These include chromoendoscopy with or without magnification endoscopy, magnification endoscopy alone, and endoscopic optical coherence tomography (5).

The American Gastroenterological Association has made recommendations for performing an upper endoscopy in selected patients based on age and history. Patients with alarm symptoms should undergo endoscopic evaluation. Alarm symptoms include weight loss, persistent abdominal pain, recurrent vomiting, dysphagia, frank or occult gastrointestinal bleeding, and anemia (6). In one study, the number of alarm symptoms correlated with the stage of the tumor. The prognosis of patients in this study worsened as the number of alarm symptoms increased, and persistent vomiting proved to be an independent predictor of poor outcome (7). Additionally, patients over the age of 45 with new-onset dyspepsia, even in the absence of alarm symptoms, should undergo upper endoscopy (6). The overall low incidence of gastric cancer in the United States makes routine screening of asymptomatic patients for detection of early gastric lesions impractical and is therefore not recommended.

Upper Gastrointestinal Series
The sensitivity of an upper gastrointestinal series has been reported to be well over 90% with advanced cancers (8), but as low as twenty percent with early gastric cancers (9). Newer techniques have improved the sensitivity of barium upper GI studies. In one study comparing conventional gastric radiography with digital radiography, the sensitivity was increased from 65% to 78% with the use of digital imaging. Digital radiography is a technology that allows immediate image display and thus faster collection of data (10).

Based on the above numbers, an upper endoscopy would be the preferred examination, but if there was a contraindication to endoscopy an upper gastrointestinal series should be performed.

Staging
Accurate staging is critical for determining optimal treatment strategies. The most commonly used staging...
system in this country is the TNM staging classification. The International Union Against Cancer (UICC) updated the TNM classification in 1997. “T” stands for tumor status, “N” stands for nodal status, and “M” stands for metastatic disease. Previously, the location of positive nodes was used to determine the N stage. The updated TNM classification system relies on the absolute number of positive nodes and divides the N groups into pN1 (1–6 positive nodes), pN2 (7–15 positive nodes), and pN3 (16 or more positive nodes). Sampling at least 15 nodes is required to accurately stage the cancer with this new classification system (11). A study examining 1,038 patients undergoing an R0 resection (negative macroscopic and microscopic margins) at a single institution analyzed the effect of positive lymph node location compared to the number of positive nodes (i.e., compared the old N staging system with the updated N staging system). In this study, the number of lymph nodes affected median survival, but the location of the lymph nodes did not. The new N categorization served as a better discriminator of median survival when fifteen or more lymph nodes were dissected (12). More recently, overall survival within each stage subgroup was shown to be dependent on the number of lymph nodes examined. For every ten extra lymph nodes examined, survival improved by 7.6% (T1/2N0), 5.7% (T1/2N1), 11% (T3N0), or 7% (T3N1) (13), strongly suggesting that sampling of a greater number of lymph nodes more accurately stages patients. In addition to showing a more significant difference in survival between each N group, the new classification has shown less deviation within each subclassification (14). Comparing the TNM classification with that of the Japanese Research Society for Gastric Cancer, both classifications perform well as prognostic indicators (15).

Computed Tomography Scan

Computed tomography (CT) scanning is useful in determining the presence of metastatic lesions associated with gastric cancer. CT scanning is inferior to EUS for staging primary tumors (20, 23). However, three-dimensional multidetector computed tomography (MDCT) is a newer technology that appears to have improved staging accuracy. A recent study showed that the overall accuracy of T stage with multidetector row CT gastrography with multiplanar reformation and virtual endoscopy was as high as 84% with an N stage accuracy of 64% (24). A study performed in Japan in 2005 demonstrated an accuracy of 86% in determining N stage for early gastric cancers using MDCT (25). A study comparing EUS with MDCT showed the T stage accuracy of EUS to be 87.5% compared to 83.3% for MDCT. The accuracy for N stage was 79.1% for EUS and 75% for MDCT (23).

Magnetic Resonance Imaging (MRI) and (18) F-2-deoxy-2-fluoro-D-glucose Positron Emission Tomography (FDG-PET) Scan

Head to head studies comparing MRI to CT consistently show MRI to have better T stage accuracy (73.3%–83% versus 66.7%–73%), but worse N stage accuracy (52%–65% versus 58%–73%) (26–28). FDG-PET scans may have a limited role in staging N status of gastric cancer, but the data is conflicting. In one study, FDG-PET had a lower accuracy for the diagnosis of locoregional nodes (N1-2) than the combination of CT scan and endoscopic ultrasound (48% vs 69%). However, the accuracy for distant nodal metastases was significantly higher for FDG-PET compared to combined CT and EUS (86% vs 62%) (29). For diagnosing locally advanced gastric cancer, the accuracy of FDG-PET is poor. In a study examining FDG-PET in the diagnosis of locally advanced gastric cancer, only 24/40 of the
Gastric Adenocarcinoma

A SPECIAL ARTICLE

Endoscopic ultrasound should be an initial diagnostic test, particularly for suspected early gastric cancers as the T stage accuracy is very high for distinguishing T1 from T2 lesions. CT scan is an important early modality as well, as this test can look for distant metastases, and as newer technology may have enhanced N staging capability. The roles of MRI and FDG-PET are still being clarified. For patients who are thought to be candidates for surgical resection based on the above studies, it would not be unreasonable to perform a laparoscopy immediately prior to planned gastrectomy to ensure patients are appropriate candidates for curative surgery.

PROGNOSIS

Between 1995 and 2001, the 5-year survival rate in the U.S. for all stages of gastric cancer was 23.2%. The 5-year relative survival rates divided by staging were as follows: 58.0% for localized, 21.9% for regional spread, and 3.1% for distant metastatic disease (35). The TNM staging classification determines which of four clinical stages a patient is in at diagnosis (Figure 2A). The 5-year survival rates for patients with resected stage II, IIIA, IIIB and IV gastric adenocarcinoma were 34%, 20%, 8%, and 7% respectively (Figure 2B) (36). Independent prognostic factors may include age and stage at diagnosis (37). In one study, however, R0 resection (negative macroscopic and microscopic margins of resection) was the only factor found to be an independent prognostic indicator (38).

(continued on page 21)
H. pylori Eradication

The role of H. pylori eradication in the prevention of gastric cancer development in humans is unclear. There are few randomized controlled studies addressing this question, and adequate follow-up using prospective studies is limited. Several studies have examined the intermediate steps of atrophic gastritis and metaplasia as endpoints, with disparate results. Most of these studies have been limited by a number of factors, as reviewed by Zivny, et al (39), including a low number of enrolled patients, inconsistent interpretation of histologic grading, different study populations, and sampling errors. Examples of different prospective study results include the following: resolution of both gastric atrophy and metaplasia with eradication therapy (40), resolution of gastric atrophy but not intestinal metaplasia (41), and neither improvement in gastric atrophy nor intestinal metaplasia (42). The largest randomized placebo-controlled trial to date, examining the effect of H. pylori eradication on the incidence of gastric cancer, was published last year by a group in China. A total of 1630 healthy carriers of H. pylori were recruited. All received endoscopy. Patients were randomized to placebo or H. pylori eradication therapy. The overall eradication rate in the treatment group was 83.7%. There were 18 new cases of gastric cancer discovered during an eight year follow-up period, with 7 cases in the treatment group and 11 cases in the placebo group (P = 0.33) However, subgroup analysis showed that in patients without precancerous lesions, eradication of H. pylori did significantly reduce the development of gastric cancer in this cohort. Precancerous lesions were defined as gastric atrophy, intestinal metaplasia, or dysplasia. Twelve patients with precancerous lesions developed gastric cancer, compared to six without precancerous lesions. Smoking and older age were independent risk factors for the development of gastric cancer in this study (43). In a more recently published 9-year prospective study from Japan, 1,787 patients who had previously undergone successful H. pylori eradication therapy were examined. Successful eradication was confirmed with follow-up endoscopy with biopsy and with a urea breath test. Gastric cancer occurred at a rate of 1.1% despite this eradication therapy. This study did not have a control group (44).

The effect of H. pylori eradication on recurrence of gastric cancer is likewise unclear, although there is data supporting its role after resection of early gastric cancer. A study published looking at the effect of H. pylori eradication on gastric cancer recurrence in patients who had undergone an endoscopic mucosal resection for early gastric cancer showed no recurring lesions in the treated group compared to a 9% recurrence rate in the untreated group (45).

In summary, eradication of H. pylori would remove the primary risk factor for the development of gastric adenocarcinoma, but the data supporting this chemoprevention strategy is lacking. There may be a point within the continuum of gastritis to neoplasmia when eradication therapy becomes ineffective, and this may explain some of the disparate results in the literature. The effect of eradication therapy in cases of established gastric adenocarcinoma is also questionable, although there is data to support its role in cases of resected early gastric cancer. Until this issue is further clarified, it is recommended that eradication therapy be given to individuals with gastric adenocarcinoma with H. pylori infection.

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Figure 2B. Stage and 5-year survival of gastric cancer in U.S.
Gastric Adenocarcinoma

A SPECIAL ARTICLE

Surgery

Resection remains the only option for cure in cases of gastric adenocarcinoma. A recent retrospective study of 2,450 patients with gastric cancer included 1,498 patients who underwent surgical resection. The 5-year survival rate for those who underwent curative resection was 51.2%. The 5-year survival rate for those who underwent resection but who were found to have residual disease or distant metastases at the time of surgery (defined as palliative resection) was only 7.8%. Of the patients undergoing palliative resection, the median survival was 15.2 months, compared to 4.6 months in the group of patients not undergoing surgery (46).

Gastric resection operations can be either in the form of a subtotal gastrectomy or total gastrectomy. With a subtotal gastrectomy, the proximal gastric remnant is anastomosed either to the duodenum or to the jejunum, whereas in a total gastrectomy the esophagus is connected directly to the small bowel. Two randomized trials demonstrated no significant difference in the 5-year survival between the two procedures when used for distal cancer (47,48), suggesting a subtotal gastrectomy should be the procedure of choice if the size and location of the tumor allows, thus avoiding the morbidity of possible splenectomy and shortening hospital stays (48). In contrast, there is data to suggest that proximal gastric cancers may be better treated with a total gastrectomy. A retrospective German study found a five-year survival rate of 22.5% for proximal gastrectomy, compared to 35.3% for total gastrectomy (49).

In cases of advanced gastric cancer, there is debate regarding the extent of lymph node dissection. A D1 dissection is defined as removal of nodal groups adjacent to the parts of the stomach removed. A D2 dissection includes celiac axis nodes and nodes of the hepatoduodenal ligament. The latter procedure is routinely performed in Japan. A relatively recent Japanese retrospective study demonstrated a 5-year survival benefit in advanced gastric cancer (390 patients) using a D2 dissection compared to D1 dissection (89.5 versus 67.6, p = 0.0279) (50). Another study published the results of 1,000 consecutive gastrectomy procedures, with D2 dissection being the standard procedure, with a 0% operative mortality in this group (51). In the United States, there has been debate regarding whether or not there is a survival benefit with D2 dissection, and whether or not there is a difference in morbidity between the two procedures. A recent meta-analysis examined the results of nonrandomized and randomized trials separately. Two randomized trials comparing the two surgeries found no survival benefit of D2 over D1 (RR 0.95) and actually showed an increased postoperative mortality for the D2 dissection (RR 2.23). Nonrandomized trials showed no survival benefit for D2, but decreased postoperative mortality (RR 0.65) (52). It has been proposed, as outlined by the authors, that the increased mortality associated with D2 dissection may be attributed to the splenectomy and pancreatectomy in a subgroup of patients undergoing this procedure, or possibly to surgical inexperience in the US relative to Japan.

For early gastric cancer (EGC), gastrectomy with lymph node dissection has a five-year survival rate of 96%. The prevalence of lymph node metastases of intramucosal cancer and cancer extending into the submucosa is reported at 3% and 20%, respectively (53). Because of the low incidence of disease outside of the gastric wall, minimally invasive surgeries, including endoscopic mucosal resection (EMR) and laparoscopic surgery have been explored in the treatment of these early gastric cancers. In a recent study from Korea, only tumor size and depth of invasion correlated with lymph node metastasis. The rate of lymph node metastasis in cases where the depth of invasion was <0.5 mm, 0.5–2.0 mm, or >2.0 mm was 9% (2/23), 19% (7/36), and 33% (15/46), respectively (P < 0.05). Though there was no statistical significance in univariate analysis, the rate of lymph node metastasis was increased as the tumor size increased (≤2 cm, 11%; 2–4 cm, 26%; >4 cm, 29%). In multivariate analysis, the tumor size (>4 cm vs ≤2 cm, odds ratio = 4.80, P = 0.04) and depth of invasion (>2.0 mm vs ≤0.5 mm, odds ratio = 6.81, P = 0.02) were significantly associated with lymph node metastasis (54). A separate study showed that lymphatic vessel invasion, histologic ulceration of the tumor, and larger size (>3 cm) were independent risk factors for lymph node metastasis. The incidence of lymph node metastasis from intramucosal EGC negative for these three risk factors was only 0.36% (55). Based on these findings, minimally invasive surgery should be used for early gastric cancer that is less than 2 cm in size, less than
0.5 mm in depth, and that lacks histologic ulceration and lymphatic vessel invasion.

Endoscopic submucosal dissection, using an insulation tipped diathermic knife, is a new technique of EMR that, by leaving the specimen en bloc, allows better T staging of the tumor (53). This technique was recently introduced in Japan and has not yet become widely available, but there is promising data regarding its use. A recent study examining this procedure in conjunction with laparoscopic lymph node dissection (LLND) in five patients not meeting criteria for EMR alone showed free margins in all cases and no complications with the lymph node dissection. The average number of removed nodes in this study was fifteen (range 6–22), and in 4 of 5 patients, the dissected nodes were free of cancer rendering the combination of EMR and LLND in these 4 patients definitive. During the mean follow-up period of 22 months, none of the 5 patients developed recurrent cancer (56).

Photodynamic Therapy

Photodynamic therapy (PDT) has also been examined as a therapeutic option in cases of early gastric cancer, particularly for patients who are not candidates for surgery. A study of 22 patients with superficial early gastric cancer receiving PDT (patients either refused surgery or were not candidates for surgery) revealed complete remission in 16/22 patients (13/16 intestinal type and 3/6 diffuse type). An average of 1.8 treatment sessions was required. The patients initially received a photosensitizing agent (mesotetrahydroxyphenylchlorin or mTHPC) and were treated 96 hours later with red light at 652 nm (20 J/cm²). A follow-up endoscopy was performed 48 hours after PDT to determine the initial therapeutic effect. Multiple endoscopies with biopsies, as well as periodic endoscopic ultrasound examinations, were performed while following these patients. The mean follow-up durations for those with intestinal-type and those with diffuse type carcinoma were 12 months and 20 months, respectively (57).

Adjuvant Therapy

The role of adjuvant therapy in gastric cancer remains unclear. As gastric cancer rate has a high recurrence rate, a number of studies have been carried out in recent years to examine the role of adjuvant therapy. More than 30 trials examining adjuvant chemotherapy versus surgery alone have been published to date, with variable results. Until recently, a significant survival advantage using post-operative chemoradiation therapy had not been demonstrated. A large gastrointestinal Intergroup Trial took place over a seven-year period beginning in 1991 with a total of 556 patients enrolled. The treatment arms were surgery alone (275 patients) and surgery plus postoperative chemotherapy (fluorouracil and leucovorin) with radiation (281 patients). The results were initially published in 2001 and updated in 2004. The only surgery related requirement in this study was resection with curative intent and en bloc resection of the tumor with negative margins (58). Median disease-free survival was 30 months for the adjuvant therapy group and 19 months for the surgery alone group (P < 0.001). The median overall survival was 35 months for the adjuvant therapy group and 26 months with surgery alone (P = .006). Based on this study, patients who undergo R0 gastric cancer resections should be offered adjuvant chemoradiation.

Peritoneal seeding of gastric cancer poses a therapeutic dilemma. Intraoperative hyperthermic peritoneal chemotherapy (IHPC) has been examined in cases of gastric adenocarcinoma for the prevention of peritoneal seeding. The rationale behind this therapy is that the chemotherapy can be more highly concentrated in the peritoneal cavity compared to serum, and it has previously been shown that the cytotoxicity of many chemotherapeutic medications is enhanced at significantly higher temperatures. (59) A Japanese study published in 1999 examined patients with surgery alone versus those who received surgery plus IHPC. IHPC in this study consisted of 3–4 liters of perfusate containing mitomycin C that was circulated in the peritoneal cavity for 120 minutes just prior to abdominal wall closure after the gastric cancer resection. The temperature ranged from 38–48 degrees Celsius. There were 71 patients in the surgery plus IHPC group and 70 in the group that underwent surgery alone. Postoperative complications were reported in 2 of the 71 patients in the IHPC group and in 2 of the 70 patients in the control group. The peritoneal recurrence (continued on page 26)
rate in the IHCP group was significantly decreased compared with that in the control group (P = 0.0000847). The 2-year, 4-year, and 8-year survival rates for the IHCP group were 88%, 76%, and 62%, respectively, whereas those for the control group were 77%, 58%, and 49%, respectively. The IHCP group had a significant survival benefit (P = 0.0362) compared with the control group (60).

Neoadjuvant Therapy
Neoadjuvant therapy is defined as therapy prior to a planned surgical resection of a cancer with the intent being to “downstage” a locally advanced tumor, thus theoretically rendering it more likely that the entire tumor is removed with surgery. This is an active area of research, and although premature, some of the data is promising. A phase III trial has shown improved survival rates as well as downstaging of T and N status with preoperative radiotherapy. The 10-year survival rate of the group receiving neoadjuvant radiotherapy was 20.26% compared to 13.30% in the surgery alone group (61). There are a number of studies examining neoadjuvant chemotherapy as well. A recently published study examining neoadjuvant chemotherapy as well. A recently published study examining the combination of cisplatin, 5-fluorouracil and folinic acid in locally advanced cancer found that 22/25 patients finished chemotherapy and 20 of these underwent laparotomy. In 13/25 patients (52%) an R-0 resection was able to be performed (62). The Dutch FAMTX trial (5-fluorouracil, doxorubicin and methotrexate) however, did not show a beneficial effect on survival, using FAMTX prior to surgery (63). Neoadjuvant chemoradiotherapy is being looked at in phase II trials, with the combination of continuous fluorouracil with external beam radiotherapy resulting in a pathologic response of 73% and a complete response of 11% thus far (64).

Another novel approach involves adding immunotherapy to chemotherapy. A study published in 2004 examined the combination of immunotherapy with BCG (bacilli Calmette-Guerin) and 5-fluorouracil, doxorubicin, and methotrexate (FAM) to FAM alone, along with a control group. BCG is used as a vaccine for tuberculosis, but it also functions as a nonspecific stimulator of the immune system. A total of 156 patients with Stage III or IV gastric adenocarcinoma were included in the trial. In patients with pT2/T3 tumors of the intestinal type, the ten-year survival was 55.3% for BCG + FAM versus 28.2% for FAM alone (P < 0.01) and 14.6% for the control group (P < 0.00018) (65).

Another novel approach is the use of a chemosensitivity test to individualize a patient’s chemotherapy regimen. Tumor cells are extracted from the patient’s tumor and used to determined sensitivity to various chemotherapeutic agents. This allows for more selective, and ideally more efficacious, therapy. In a study examining patients with stage IV disease, the five-year survival was 38.1% in the chemosensitivity-guided chemotherapy arm compared to 0% in the standard chemotherapy and no chemotherapy arms (66).

Palliation
Palliation is obviously an important component of any treatment strategy for advanced gastric cancer. Many patients need therapy for bleeding or obstructing lesions, as well as for such complications as fistulae. Endoscopic therapy includes enteral stent placement or laser therapy for obstructing lesions, and argon plasma coagulation for hemostasis (67). Palliative surgery may also be necessary, such as a bypass procedure for gastric outlet obstruction (68), and may offer a limited survival benefit in selected patients (46).

CONCLUSION
Early recognition of gastric adenocarcinoma and accurate staging are essential to afford a patient the best chance of survival. Although H. pylori is the most important causative agent in the pathogenesis of gastric adenocarcinoma, the role of eradication therapy in preventing gastric carcinogenesis needs to be clarified. Surgery remains the mainstay of treatment. The optimal form of surgical resection likely depends on cancer location, but regardless surgical resection remains the only potential cure of gastric adenocarcinoma. The optimal type of lymph node dissection is still being debated and study results differ between Japan and Western countries. What appears more important than location is the number of lymph nodes removed, and the current TNM classification takes this into account. Neoadjuvant therapy is a promising newer treatment modality and
various combinations of adjuvant therapies for gastric adenocarcinoma continue to be studied.

References


Gastric Adenocarcinoma

A SPECIAL ARTICLE