HHS Public Access

Author manuscript

Gastroenterol Clin North Am. Author manuscript; available in PMC 2015 June 15.

Published in final edited form as:

Gastroenterol Clin North Am. 2013 June ; 42(2): 337–357. doi:10.1016/j.gtc.2013.01.010.

Surgical Considerations in the Treatment of Gastric Cancer

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Keywords

Gastric cancer; Staging; Resection; Margins; Palliation; Neoadjuvant chemotherapy

INTRODUCTION

Despite steady declines in the incidence and mortality, gastric cancer is the 5th most common malignancy diagnosed in developed countries in both men and women, with more than 270,000 new diagnoses in 2011. More than 180,000 deaths from gastric cancer were reported for the same year, reflecting a high cancer-related mortality rate.[1] Fatality rates are high in most countries (overall mortality approximately 70%–90%) except in Japan (40%), and stomach cancer ranks 2nd as a cause of cancer-related death. Surgical resection remains the treatment of choice for gastric cancer. Improvements in multimodal chemotherapy and radiotherapy, however, have influenced clinical decision making and treatment algorithms. The largest reported experience in the surgical treatment of gastric cancer originates from the East Asia, especially Japan and Korea. New data from Western centers have reproduced many of these findings. This review aims to evaluate the role of surgery in the staging, resection, and palliation of gastric cancer.

GASTRIC CANCER STAGING

Histologic Staging

Staging of gastric cancer is according to depth of invasion (T stage), number of lymph node metastases (N stage), and presence of distant disease (M stage). Starting January 1, 2010, newly diagnosed gastric cancers were to be staged using the 7th edition of the TNM staging system (Table 1).[2,3] The differences between the 6th and 7th editions specifically regarding gastric cancer pertain mostly to depth of tumor invasion, including

- T1 subdivided to delineate mucosal versus submucosal lesions

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Disclosures: None to declare.

- T2a and T2b changed to T2 and T3 to represent muscularis propria and subserosa invasion, respectively
- T3 and T4 changed to T4a and T4b to represent serosal perforation and invasion of adjacent structures, respectively

Historically, the Siewert criteria published in 1998 have been used to classify adenocarcinomas arising at or near the gastroesophageal junction (GEJ)[4]:

- Type I: lesion of the distal esophagus, 1–5 cm proximal to the GEJ
- Type II: lesion arising within the GEJ, within 1 cm proximal and 2 cm distal to the GEJ
- Type III: Lesion arising 2 cm to 5 cm distal to the GEJ with invasion into the esophagus

As part of the 7th edition of the TNM staging system, GEJ adenocarcinomas were also reclassified as follows:

- A lesion with its center within 5 cm of the GEJ and with extension into the esophagus is staged using esophageal carcinoma criteria.
- A lesion with its center within 5 cm of the GEJ but without extension into the esophagus, and a lesion with its center greater than 5 cm away from the GEJ are staged using gastric carcinoma criteria.

To evaluate the clinical effects of the new TNM staging system, Suh and colleagues[5] retrospectively reviewed adenocarcinoma of the GEJ in 497 patients operated on with curative intent based on Siewert classification, from 2003 to 2009. On analysis of staging, 11 of 230 (4.6%) lesions that before would have been classified as TNM stage I under gastric guidelines were upstaged to TNM stage II esophageal lesions. The 5-year survival rates of gastric TNM stage I and esophageal TNM stage II in this study were 92.1% and 90.6%, respectively. Meanwhile, 20 of 125 (16.0%) gastric TNM stage II cancers were upstaged to esophageal TNM stage III cancers. The 5-year survival rates of gastric TNM stage II and esophageal TNM stage III in this study were 84.6% and 51.4%, respectively. The investigators argued that the new guidelines did not adequately distinguish GEJ tumors, because upstaging did not correlate with clinical outcomes.

Surgical Staging

Two-thirds of patients with gastric cancer in the United States present with advanced disease, and the majority show no significant findings on physical examination. The development of specific physical signs usually indicates metastatic disease.

For years, laparotomy was the standard surgical procedure for staging. On gross inspection, the decision between a resection with curative intent versus a nontherapeutic or noncurative procedure was made based on nodal disease, extension into adjacent organs, or distant metastasis. Preoperative CT scans and MRI have not been able to detect noncurative disease in all patients. As technology has progressed, new staging modalities have emerged, including staging laparoscopy, endoscopic and intraoperative ultrasound, and peritoneal

washings for cytology. With advances made in neoadjuvant chemotherapy, minimally invasive staging methods have become more important for optimal management.

Staging laparoscopy was compared with preoperative staging CT scan by Burke and colleagues.[6] Between 1990 and 1995, 103 patients with newly diagnosed gastric adenocarcinoma and no evidence of intra-abdominal metastatic disease on CT scan underwent staging laparoscopy. Sixty contemporary patients who underwent staging laparotomy were selected from the same prospective database as a control. Frozen sections were taken of suspicious lesions to evaluate for metastasis: 32 (31.1%) had biopsy-proved metastatic disease and 71 had no laparoscopic evidence of metastasis, of whom 6 (8.5%) had metastases on laparotomy (n = 3) or in distant lymph nodes after resection (n = 3). In this study, staging laparoscopy had a sensitivity of 94%and a specificity of 100%. Patients with metastatic disease confirmed during laparoscopy avoided the unnecessary morbidity of laparotomy. Karanicolas and colleagues[7] reviewed the Surveillance, Epidemiology and End Results cancer database to analyze frequency of staging laparoscopy in the general population. Patients over 65 years of age diagnosed with gastric adenocarcinoma between 1998 and 2005 who underwent a surgical procedure related to gastric cancer were identified. Of 6388 patients, 506 (8%) underwent staging laparoscopy, of whom 306 (60%) underwent therapeutic intervention, 49 (10%) proceeded to laparotomy but no therapeutic procedure, and 151 (30%)underwent only laparoscopy. Use of staging laparoscopy increased over time (5.5% in 1998 to 11.1%in 2005,$P<.01$), and patients tended to be young and white, living in the Northeast, and with proximal cancers, and they had fewer comorbidities than those who did not undergo staging laparoscopy. Although increasing in use, staging laparoscopy seems to remain underutilized in its potential benefit of avoiding unnecessary laparotomy.

To evaluate endoscopic ultrasound (EUS) compared with staging laparoscopy, Power and colleagues[8] prospectively reviewed patients being evaluated for neoadjuvant chemotherapy. Between 2003 and 2005, 94 patients without evidence of metastatic disease on staging CT scan or MRI were analyzed. Those with T1–2 and N0 lesions on EUS were considered low risk for M1 disease (n = 26), and those with T3–4 or N+ were considered high risk (n = 68). Those deemed high risk by EUS most often had tumors at the GE junction or gastric cardia. Staging laparoscopy detected M1 disease in 18 (19%) patients, of whom 17 had been high risk by EUS; the other patient was low risk by EUS but had linit is plastica, which some investigators consider high risk in and of itself. In this study, EUS was 89% sensitive (95% CI, 67%–99%) and 100% specific (95% CI, 95%–100%) in predicting M1 disease when followed by staging laparoscopy. This compared favorably with staging laparoscopy alone, with sensitivity 95% (74%–100%) and specificity 100% (95%–100%). The investigators suggest that in centers with sufficient experience, high-risk lesions on EUS may be a deciding factor in who requires a staging laparoscopy to limit unnecessary or low yield procedures. Often-present esophageal strictures, however, may limit the application of EUS.

EUS cannot assess the presence of liver or retroperitoneal metastasis. Smith and colleagues[9] prospectively evaluated the benefit of laparoscopic ultrasound (LUS) when added to staging laparoscopy for esophageal and gastric cancers. After standard noninvasive staging work-up, patients with potentially resectable disease underwent complete staging laparoscopy followed by LUS. Of 93 patients, 18 (19.4%) were considered unresectable on staging

laparoscopy. Of the remaining 75 patients, 9 (12.0%) were determined unresectable on LUS—4 with esophageal cancer had celiac and para-aortic lymph node disease and 5 with gastric cancer had liver metastases, liver or pancreatic invasion, or celiac and para-aortic lymph node disease. Staging laparoscopy and LUS had a combined 29.0% reduction in unnecessary laparotomy. The investigators concluded that LUS provides a small added benefit to staging laparoscopy in preventing low-yield laparotomy. Hulscher and colleagues[10] narrowed their evaluation of LUS to adenocarcinoma of the gastric cardia with distal esophageal involvement. Between 1995 and 1999, 48 patients with potentially resectable disease on preoperative imaging underwent staging laparoscopy with LUS. Laparoscopy detected distant metastases in 7 (14.6%) and LUS detected distant metastases in an additional 4 (8.3%) patients, resulting in a combined 23% reduction in unnecessary laparotomy.

Bentrem and colleagues[11] evaluated peritoneal cytology as a predictor of poor outcomes before attempted gastric cancer resection. Between 1993 and 2002, 371 patients underwent staging laparoscopy with peritoneal lavage cytology performed before undergoing R0 resection; 24 (6.5%) had positive cytology, which was associated with T stage (10% of T3–4 vs 2% of T1–2; $P = .02$) and overall stage (11% of stage III, 7% of stage II, 2% of stage I; $P = .002$). On multivariate analysis, poorer overall survival was associated with positive cytology (relative risk 2.7, $P<.001$), distal tumor location, and preoperative T stage and N stage. The investigators suggest that peritoneal lavage cytology should be considered in assessing a patient's prognosis after attempted curative resection. Mezhir and colleagues[12] re-evaluated outcomes of gastric cancer patients with positive cytology, because the TNM 7th edition considers positive peritoneal lavage equivalent to M1 disease. Patients who had undergone staging laparoscopy with positive peritoneal lavage between 1993 and 2009 were included whereas those with as cites or who had undergone chemotherapy were excluded. Of the 291 patients included, 198 (68%) had gross peritoneal disease or visceral metastases seen on staging laparoscopy. In the remaining 93 patients, only positive peritoneal cytology indicated M1 disease. Median overall survival was 1 year, with 80% mortality at that time. Patients with gross metastatic disease had poor disease-specific survival, and those with positive cytology fared only slightly better. Peritoneal cytology, particularly for patients without evidence of gross metastasis, should be factored into the decision of whether to proceed with resection.

EXTENT OF GASTRIC RESECTION

Distal Disease

For years, there was debate over subtotal gastrectomy (SG) versus total gastrectomy (TG) as the optimal procedure for gastric antrum malignancies. Gouzi and colleagues[13] published the first randomized study comparing SG and TG for distal lesions in 1989. From 1980 to 1985, 169 patients of any age with a potentially curable distal gastric malignancy underwent either SG or TG, without routine splenectomy. SG and TG were similar in terms of perioperative morbidity (34% vs 33%) and mortality (3.2% vs 1.6%). Overall 5-year survival was 48%, similar to contemporary Western retrospective studies. Nodal involvement and serosal invasion were associated with survival, whereas extent of resection

was not. Although the trial suffered from a small study population, the investigators concluded that SG was a viable treatment option for distal gastric cancer.

Bozzetti and colleagues[14] conducted a larger randomized controlled trial to compare SG and TG. Patients with distal cancers underwent staging laparotomy to confirm that the location of the primary lesion was at least 6 cm away from the gastric cardia and that there was no N3 disease or unresectable disease. From 1982 to 1993, 624 patients were included, 320 in the SG group and 306 in the TG group. All underwent D2 dissection, splenectomy was optional, and 6-cm margins were obtained when possible. Although perioperative mortality was similar between SG and TG (1.3% vs 2.3%, $P = .27$), morbidity was greater in the TG group (15.5% vs 10.3%, $P = .05$), which was attributed to complications associated with splenectomy. Mean length of stay was improved in the SG group (13.8 days vs 15.4 days, $P<.001$). Bozzetti and colleagues[15] subsequently published 5-year survival data as well as descriptive data. Results of permanent sections revealed R1 resection in 15 (4.7%) patients in the SG group versus 6 (2%) patients in the TG group. Only 10 patients overall received adjuvant chemotherapy. Patients with larger tumors, higher tumor grade, and nodal involvement fared worse. Five-year survival rates between SG and TG were similar (65.3% vs 62.4%; hazard ratio [HR] 95% CI not significant).

Because the aforementioned studies did not include data on number of lymph nodes dissected and because the range of tumor grade was variable, de Manzoni and colleagues[16] conducted a prospective multicenter trial comparing SG with TG in patients with a T3 lesion of the gastric antrum. During 1996, 117 patients who underwent potentially curative surgery with D2 dissection were analyzed; 77 (65.8%) underwent SG whereas 40 underwent TG without splenectomy. Overall perioperative morbidity (14.5%) and mortality (2.6%) were not associated with extent of resection. The median number of lymph nodes dissected was 30. Median survival was improved in the SG group (38 months vs 23 months, $P = .011$) as was 5-year survival (36% vs 22%). On multivariate analysis, only nodal disease was independently associated with survival. The study was limited in that it was not randomized, and surgeon preference had an effect in that elderly patients were more likely to undergo SG instead of TG. It seemed, however, that even in distal lesions involving the serosa, performing SG instead of TG had no adverse effect on survival.

One of the primary arguments in favor of SG over TG when possible was the effect on quality of life. Davies and colleagues[17] evaluated 47 consecutive patients who had presented with gastric cancer and underwent potential R0 resection. TG was performed for lesions of the proximal and middle thirds of the stomach (n = 26), and SG was performed for those of the distal third (n = 21). D2 dissection was performed, and the spleen and pancreas were preserved when possible. No patient received adjuvant chemotherapy. Quality of life was assessed preoperatively and at 1, 3, 6, and 12 months postoperatively using 5 validated questionnaires. The interviewer was blinded to the procedure the patient had received. Of the 5 assessment tools used, only the Rotterdam symptom checklist and the Troidl index achieved a statistically significant difference between the SG and TG groups through 12 months postoperatively. Each one indicated improved quality of life in the SG group over the TG group.

Based on approximately equivalent long-term survival rates, generally higher operative morbidity and mortality of patients undergoing TG, and improved quality of life for patients undergoing SG, for distal gastric cancer the procedure of choice is SG, provided that adequate proximal margins of 5 cm to 6 cm are able to be obtained.

Proximal Disease

The adequacy of proximal gastrectomy (PG) versus TG for tumors of the proximal one-third of the stomach has been the subject of various studies. Harrison and colleagues[18] published one of the first studies to evaluate the long-term outcomes of each procedure. Between 1985 and 1995, 98 patients underwent surgery other than esophagogastrectomy for proximal tumors; 65 (66%) patients underwent PG and 33 underwent TG, all via an abdominal approach. Tumor differentiation and stage were similar between the groups, but tumor size was larger in the TG group (7 cm vs 4 cm, $P = .02$) and more lymph nodes were harvested. Proximal margins were similar between the groups, but distal margins were improved in the TG group (6.5 ± 1.2 cm vs 3.9 ± 0.5 cm, $P<.05$). Overall 5-year survival was similar (41% in TG vs 43% in PG). Kim and colleagues[19] retrospectively reviewed patients who underwent either PG or TG for proximal gastric cancer. PG was performed only when the cancer was limited to the proximal one-third. Between 1992 and 2000, 43 patients underwent PG and 104 underwent TG. Thoracotomy was performed in 3 PG (7.0%) and 7 TG (6.7%), splenectomy and distal pancreatectomy in 18 PG (41.8%) and 15 TG (14.4%), and splenectomy alone in 8 PG (18.6%) and 13 TG (12.5%). The groups were fairly well matched for tumor characteristics, including size and differentiation, although all T4 lesions were resected via TG. The majority of the PG group underwent D1 dissection, whereas the majority of the TG group underwent at least D2 dissection. The PG group experienced higher perioperative morbidity (48.8% vs 14.4%, $P<.001$), most commonly anastomotic strictures, and higher rate of recurrence (39.5% vs 4.8%, $P<.001$). Overall 5-year survival was similar (48.6% in TG vs 46.0% in PG, $P = .972$). This remained true for stage I or stage II disease; however, for stage III disease, 5-year survival after TG was significantly improved (38.4% vs 17.1%, $P = .035$). Therefore, given higher rates of concomitant organ resection and perioperative morbidity as well as more challenging D2 dissection, PG could only be recommended for early gastric cancer with adequate margins and limited nodal involvement.

Regarding management specifically of proximal early gastric cancer, An and colleagues[20] compared PG with TG. From 2000 to 2005, 423 patients underwent PG (n = 89 [21.0%]) or TG (n = 334 [79.0%]) for stage I or stage II proximal gastric adenocarcinoma. The TG group had larger tumors (4.0 cm vs 2.5 cm, $P<.001$) and more mean lymph nodes harvested (39.1 vs 22.4, $P<.001$). PG was associated with higher morbidity (61.8% vs 12.6%, $P<.001$), most often anastomotic stenosis and esophageal reflux, and these were successfully treated with balloon dilatation. Five-year survival was similar between the 2 groups (99.2% in PG vs 98.5% in TG, $P = .57$), as were long-term body weight and nutritional markers. The investigators could not recommend PG over TG for proximal early gastric cancer based on the frequency of postoperative complications.

Resection of Adjacent Organs

Although direct tumor involvement of the spleen or distal pancreas warrants resection to achieve potential R0 resection and remove pathologic lymph nodes, routine splenectomy and distal pancreatectomy as part of a D2 dissection adds early morbidity without a proven long-term survival benefit. The most common complications cited are postoperative infection and pancreatic fistula. Yu and colleagues[21] made one of the clearest arguments against routine splenectomy. Between 1995 and 1999, patients undergoing TG for proximal gastric adenocarcinoma were randomized to undergo splenic resection versus preservation. Those with pancreas or spleen invasion, gastrosplenic ligament involvement, or hilar or splenic artery lymph node disease were excluded. Of 207 patients who met criteria, 104 (50.2%) underwent splenectomy. The resection and preservation groups had similar perioperative morbidity (15.4% vs 8.7%, $P = .142$) and mortality (1.9% vs 1.0%), median length of stay (11 days in each group), median number of harvested lymph nodes (40 in each group), and overall 5-year survival (54.8% vs 48.8%, $P = .503$). With no survival benefit or improved lymph node yield, routine splenectomy could not be recommended.

To evaluate extension of gastric cancer resection to adjacent organs, Shchepotin and colleagues[22] retrospectively reviewed 353 patients who underwent multiorgan resection of T4 gastric cancers between 1974 and 1994. Resection of adjacent organs was based on gross appearance; permanent section revealed that 39 (11%) had desmoplastic reactions instead of direct tumor invasion. Patients with tumors localized to the distal one-third or the cardia underwent SG (n = 237, 67.1%) and the remainder underwent TG (n = 116, 32.9%). N1 or N2 lymph node involvement was present in 137 (38.8%) patients. Transverse colectomy was performed in 159 (45.0%) patients, combined splenectomy and distal pancreatectomy in 150 (42.5%), left hepatic lobectomy in 101 (28.5%), and proximal pancreatectomy in 37 (10.5%). Overall, 254 (71.9%) had 1 extra organ removed, 73 (20.7%) had 2 removed, and 26 (7.4%) had 3 or more resected. Perioperative morbidity was 31.2% (most commonly intra-abdominal abscess) and mortality was 13.6%. Overall 5-year survival was 25%, 37% among node-negative patients versus 15% among node-positive patients. Number or type of organ resected did not affect survival.

Martin and colleagues[23] retrospectively reviewed adjacent organ resection among R0 resections from 1985 to 2000. Of 1133 patients who underwent PG, SG, or TG, 865 underwent gastrectomy alone whereas 268 underwent gastrectomy with additional organ resection. Additional organ resection was more common with proximal cancers, and more often TG was performed. The most common additional organs resected were spleen (45.9%), spleen and pancreas (14.2%), spleen and colon (6.7%), colon (6.0%), pancreas (4.5%), and other (22.8%). Additional organ resection was associated with more-invasive cancers and increased nodal involvement. Postoperative mortality was similar even with additional organ resections (3.7% vs 3.6%). Five-year survival for the additional organ resection group was 32%, similar to contemporary studies; on multivariate analysis, T stage and N stage were independently associated with survival, whereas number or type of additional organs resected was not. Risk of recurrence was, however, higher in the additional resection group (52% vs 42%, $P = .003$). With appropriate identification of T3 or

T4 tumors, the investigators recommended additional organ resection due to its potential benefit and low additional morbidity and mortality.

Several subsequent series have supported the role of extended organ resection for patients who have potentially curable disease (Table 2). Kobayashi and colleagues[24] retrospectively reviewed patients presenting between 1993 and 2000, 82 of whom had invasion into adjacent organs. Extended resections included distal pancreatectomy and splenectomy (n = 36), transverse colectomy (n = 35), and other (n = 34). Some patients underwent noncurative resections due to peritoneal dissemination or liver or distant lymph node involvement. The most common postoperative complication was pancreatic fistula. Kunisaki and colleagues[25] retrospectively reviewed 117 patients with T4 gastric adenocarcinoma undergoing surgery from 1994 to 1999. Thirty-eight (32.5%) were attempted curative resections, whereas the remainder were noncurative in intent due to peritoneal dissemination, liver or para-aortic involvement, positive margins, distant metastasis, or unresectable bulky lymph node disease. The most commonly involved organs were pancreas (52.1%), transverse colon (37.6%), and liver (8.5%). Fifteen (12.8%) patients underwent multiple additional organ resections. The most common postoperative complication was pancreatic fistula. Carboni and colleagues[26] performed a similar retrospective review, identifying 65 patients with advanced gastric adenocarcinoma undergoing surgery between 1979 and 2004. Extended resections included spleen (n = 31), pancreas (n = 28), colon (n = 16), and other (n = 24). Desmoplastic reaction instead of tumor invasion was confirmed in 13 (20%) patients. Medical complications produced half of the operative morbidity and an additional 7 perioperative deaths. Other small series have been published but do not report 5-year mortality, limiting comparison.

Resection of Gastroesophageal Junction Tumors

Although it is generally accepted that Siewert type I tumors are best treated by esophagectomy, the optimal surgical management of proximal gastric tumors, grades II and III, has been debated. Ito and colleagues[27] retrospectively reviewed the charts of all patients with Siewert type II or III lesions presenting between 1991 and 2001; 82 patients were included for analysis, 59 (72.0%) had Siewert type II lesions and 23 (28.0%) had type III lesions. Operative management consisted of 27 (33%) total esophagectomy (mostly transthoracic), 24 (29%) extended gastrectomy with thoracotomy, and 31 (38%) extended gastrectomy without thoracotomy. More patients with type II cancer had received neoadjuvant chemotherapy than those with type III cancer. Overall perioperative mortality was 2.4% and morbidity was 20%. Morbidity among the esophagectomy group was higher (33% vs 11%, $P = .014$), and thoracotomy had no significant effect on morbidity in the extended gastrectomy group (13% with vs 10% without, $P = .74$). There was no significant difference in tumor grade, T stage, or N stage between esophagectomy and gastrectomy groups. Overall mean number of lymph nodes resected was suboptimal (median 6), but 65% were determined to have an R0 resection. Those who underwent extended gastrectomy had positive margins more frequently (38% vs 7%, $P = .04$), and this was associated with T3 and T4 lesions. Margin information was used to determine that the optimal proximal gross margin length was 6 cm and the distal margin length 4 cm. Five-year mortality was similar among the 3 groups (esophagectomy 30%, extended gastrectomy with thoracotomy 23%, extended gastrectomy without thoracotomy 34%; $P = .16$). On multivariate analysis, positive

margins, increased patient age, and nodal disease were independently associated with poorer survival. The investigators recommended whichever surgical approach would best achieve adequate gross margins and improved lymph node harvesting.

Laparoscopic Gastric Resection

In recent years, surgeons have been performing laparoscopic-assisted or robotic-assisted gastric cancer resections, but laparoscopic extended lymph node dissection is technically challenging and requires experience. To assess the adequacy of totally laparoscopic SG, Huscher and colleagues[28] conducted a randomized prospective trial comparing laparoscopic and open approaches. Between 1992 and 1996, 59 patients with distal gastric cancer underwent either open or laparoscopic SG with D1 or D2 dissection and Roux-en-Y or Billroth II reconstructions. No patient from the laparoscopic group was reported to have port site metastasis on followup. The laparoscopic group had less operative blood loss (229 mL vs 391 mL, $P<.001$), shorter length of stay (10.3 days vs 14.5 days, $P<.001$), and quicker return to diet (5.1 days vs 7.4 days, $P<.001$). Differences in perioperative morbidity (26.7% vs 27.6%) and mortality (3.3% vs 6.7%) and overall 5-year survival (58.9% vs 55.7%) were not statistically significant. Lee and colleagues[29] demonstrated similar benefits by prospectively analyzing 34 patients with distal lesions less than 5 cm and without significant serosal involvement who had undergone potentially curative laparoscopic gastrectomy between 1998 and 2005, matching them to 34 patients who had undergone open surgery for similar pathology. No patients were converted from laparoscopic to open. Mean operative time (283 minutes vs 195 minutes, $P<.001$) was longer in the laparoscopic group, whereas estimated blood loss (74 mL vs 190 mL, $P<.001$), return of bowel function (2.9 days vs 4.9 days, $P<.01$), and length of stay (8.5 days vs 12.1 days, $P<.001$) were all improved in the laparoscopic approach compared with open surgery. Perioperative morbidity and survival during follow-up were similar.

To compare laparoscopic with open SG and TG, Moisan and colleagues[30] prospectively analyzed 31 patients who had undergone laparoscopic SG or TG for adenocarcinoma between 2005 and 2010. The 31 patients were case-matched by randomly selecting patients from the open surgery group with similar T stage, extent of gastrectomy, age, and gender. All included patients who lived longer than 30 days postoperatively, achieved R0 resection, had at least D1 dissection, did not undergo splenectomy or pancreatectomy, and did not have neoadjuvant chemotherapy. Patients were fairly evenly distributed by stage (I–III) and tumor location (upper vs middle vs lower third); 22 patients in each group underwent TG and 9 underwent SG. As before, the laparoscopic group experienced longer mean operative time (250 minutes vs 210 minutes, $P = .007$), less mean estimated blood loss (100 mL vs 300 mL, $P<.001$), faster return to diet (4 days vs 7 days, $P<.001$), and shorter length of stay (7 days vs 10.5 days, $P = .001$). Perioperative morbidity was identical (12.9%) and the difference in median number of retrieved nodes was nonsignificant (35 vs 39). Overall 3-year survival was not significantly different (82.3% vs 86.9%, $P = .557$).

The laparoscopic approach specifically for proximal gastric tumors was retrospectively reviewed by Ahn and colleagues.[31] Between 2003 and 2009, 131 patients underwent either laparoscopic PG (LAPG) or laparoscopic TG (LATG). Fifty patients underwent LAPG and

81 underwent LATG; a common reason to perform LATG instead was a tumor size too large to provide a remnant of sufficient capacity to allow return of postoperative gastric function. Patient demographics between the groups were similar. LAPG patients experienced shorter operative time and less blood loss as well as lower rate of splenectomy (0 vs 6). All LAPG and most LATG patients (86.4%) underwent D1 dissection. The LAPG group had similar staging compared with the LATG group but smaller tumors (2.8 ± 1.3 cm vs 4.0 ± 2.7 cm, $P = .002$), shorter proximal margins (3.5 ± 2.3 cm vs 4.4 ± 2.3 cm, $P = .038$) and distal margins (4.0 ± 1.6 cm vs 14.3 ± 4.2 cm, $P<.001$), and fewer mean harvested lymph nodes (33.1 vs 47.4, $P<.001$). Return to diet, return of bowel function, hospital length of stay, and early morbidity were similar. Late morbidity among the LAPG group, however, was higher (44.0% vs 22.2%, $P = .005$), most commonly reflux symptoms or anastomotic stenosis. This joins a growing body of data that demonstrates similar long-term outcomes between open and laparoscopic approaches for the resection of gastric tumors.

Role of Endoscopic Resection

Two endoscopic treatment modalities are in wide use today in Eastern centers and selectively used in Western centers: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Originally, Japanese guidelines indicated EMR for less than 2 cm, well-differentiated, nonulcerated gastric cancer lesions confined to the mucosa before they invaded the submucosa and subsequently the lymphatic system.[32] Later, guidelines were expanded to include differentiated, nonulcerated mucosal cancer greater than 2 cm; differentiated, ulcerated mucosal cancer up to 3 cm; and undifferentiated, nonulcerated, mucosal cancer up to 2 cm. After excision of the lesion using these techniques, histologic staging is used to determine adequacy of the excision and need for subsequent surgery.

These endoscopic techniques must be carefully applied, however. Ishikawa and colleagues[33] retrospectively reviewed the histology specimens of resections with D2 dissections for early gastric adenocarcinoma from 1980 to 2004. Of 278 specimens, 156 were mucosal and 122 were submucosal lesions. Ulceration was present in 41 (26.3%) of mucosal cancers, of which 6 (14.6%) also had lymph node metastasis, all only to the N1 tier. Ulceration was present in 21 (18.3%) of submucosal cancers, of which 10 (47.6%) had lymph node involvement. Of the 101 nonulcerated submucosal cancers, however, 18 (17.8%) had nodal disease. Overall, 3 cases that would have met extended criteria for EMR or ESD were found to have lymph node metastasis, which has been shown the major prognostic factor in early gastric cancer. The investigators suggest that the safest use of EMR/ESD is for nonulcerated mucosal lesions of any size and ulcerated mucosal lesions less than 2 cm in diameter.

LYMPH NODE DISSECTION

One of the best-known and earliest randomized trials to evaluate extent of lymph node dissection is by the Dutch Gastric Cancer Group. Bonenkamp and colleagues[34] published initial results of the Dutch D1D2 trial, a prospective, randomized controlled trial conducted from 1989 to 1993. Inclusion required histologic confirmation of gastric adenocarcinoma without evidence of distant metastasis. Eleven supervising surgeons were involved, determining if curative resection was possible based on gross appearance and frozen section of para-aortic lymph node biopsy. Patients underwent either SG, if 5-cm margins could be

achieved, or TG. D1 dissection was defined as including the N1 tier (perigastric) lymph nodes whereas D2 dissection included dissection of lymph nodes in the N2 tier. Of 1078 patients originally randomized, 711 were operated on with curative intent, 380 in the D1 group and 331 in the D2 group; 41 (11%) of the D1 group underwent splenectomy compared with 124 (38%) of the D2 group, and distal pancreatectomy was performed in 10 (3%) of the D1 group versus 98 (30%) of the D2 group. Perioperative mortality was significantly higher in D2 patients (10% vs 4%, $P = .004$), as was morbidity (43% vs 25%, $P<.001$), rate of reoperation (18% vs 8%, $P<.001$), and average length of stay (25 days vs 18 days, $P<.001$). Bonenkamp and colleagues[35] later published 5-year survival data. Of 589 patients who achieved R0 resection and survived the operative hospital stay, 324 underwent D1 and 265 underwent D2 dissection. The risk of relapse at 5 years in the D1 group was higher (43% vs 37%), but the 95% CI failed to achieve statistical significance ($P = .22$). Overall survival rates between the 2 groups were similar (45% in D1 vs 47% in D2), and the HR 95% CI failed to achieve significance. At this point, resection with D2 dissection showed no clear benefit over D1 dissection for curative resection of gastric cancer in Western countries. Hartgrink and colleagues[36] published 10-year survival data and Songun and colleagues[37] reported 15-year survival data. Overall survival rates were similar between D1 and D2 dissection at 10 years (30% vs 35%, $P = .53$) and 15 years (21% vs 29%, $P = .34$). The long-term follow-up data confirmed the previous conclusion of no clear survival benefit of D2 dissection over D1 dissection.

Cuschieri and colleagues[38] reported initial results of the Medical Research Council (MRC) prospective, randomized controlled trial evaluating D1 versus D2 dissection, a parallel United Kingdom study. Inclusion criteria were histologically confirmed gastric adenocarcinoma with potential for curative resection. All patients underwent staging laparotomy, including examination of para-aortic lymph nodes. Those with potentially curable disease were randomized intraoperatively to resection with either D1 or D2 dissection. D1 dissection involved those nodes within 3 cm of the primary tumor along with omentum, whereas D2 dissection added celiac axis, hepatoduodenal, retroduodenal, splenic, and peripancreatic lymph nodes. SG was performed for antral tumors if a 2.5-cm proximal margin was possible; all others underwent TG. Over a 7-year period, 400 patients were deemed eligible at laparotomy and were randomized. As with the Dutch trial, the D2 group experienced higher perioperative morbidity (46% vs 28%, $P<.001$) and mortality (10.5% vs 4.5%, $P<.04$) and longer length of stay (23 days vs 18 days, $P = .01$). Cuschieri and colleagues[39] later reported survival data, showing similar overall 5-year survival between D1 and D2 (35% vs 33%, $P = .43$). This correlated with conclusions from the Dutch trial.

The aforementioned trials were performed when D2 dissection frequently involved splenectomy and/or distal pancreatectomy, the portions of the procedure to which the higher morbidity and mortality of D2 versus D1 dissection had been attributed. Subsequent studies have analyzed a limited or modified D2 dissection compared with either D1 or standard D2 dissection. Edwards and colleagues[40] prospectively evaluated D1 versus spleen-preserving D2 dissection. The study consecutively enrolled patients with histologically confirmed gastric adenocarcinoma with potential for curative resection based on staging laparoscopy. Of 118 potentially curable patients, 36 presented to one surgeon and were treated with

resection plus D1 dissection, whereas 82 presented to the other surgeon and were treated with resection and modified D2 dissection. Extent of dissection for each group was similar to previous studies, except that nodes were dissected off the splenic artery, and splenectomy was only performed for hilar involvement. In this limited study, perioperative mortality was similar between the D1 and modified D2 groups (8.3% vs 7.3%, $P = 0.848$), but 5-year survival was improved in the modified D2 group (59% vs 32%, $P = .039$). On univariate analysis, splenectomy and pancreatectomy were not associated with survival. On multivariate analysis, however, extent of lymphadenectomy was associated with survival, suggesting a survival benefit of the modified D2 dissection over the standard D1 dissection.

Degiuli and colleagues[41] published initial results of the Italian Gastric Cancer Study Group's experience in pancreas-preserving D2 dissections. The study was conducted from 1994 to 1996, in an effort to decrease the Western operative morbidity and mortality of standard D2 dissections with distal pancreatectomy. After staging laparotomy demonstrated no gross metastatic disease or pathologic N3 or N4 lymph nodes, 191 patients underwent SG or TG with D2 lymph node dissection. The distal pancreas was spared in TG when there was no direct tumor invasion. Perioperative morbidity (20.9%) and mortality (3.1%) compared favorably with contemporary Eastern center results. Degiuli and colleagues[42] later published 5-year survival data. Overall survival was 55% and disease-free survival was 65%, which were improved compared with the Dutch and MRC results. Specific data on how many distal pancreatectomies were performed, however, were not included and the effect of European surgeons' increased experience in performing D2 dissection was unable to be assessed.

Building on previous experience, Degiuli and colleagues[43] designed a multicenter randomized controlled trial to evaluate D1 versus modified D2 dissection in specialized Western centers. From 1998 to 2005, 267 patients with potentially curable disease based on staging laparotomy, using peritoneal lavage and lymph node biopsy at the left renal vein, were randomized to SG or TG with either D1 or modified D2 dissection. The study faced some difficulty with enrollment due to the perception that D2 dissection was the superior treatment, causing many eligible patients to decline randomization. Only surgeons involved with the previous Italian Gastric Cancer Study Group trial were included. Of patients who underwent TG with D2 dissection, 12 of 31 underwent splenectomy and 2 of 31 underwent distal pancreatectomy. The study found no significant differences between D1 and D2 dissection in perioperative morbidity (12.0% vs 17.9%, $P = .178$) or mortality (3.0% vs 2.2%, $P = .722$) or length of stay (12.8 days vs 13.1 days, $P = .732$). These results were improved over the earlier Dutch and UK trials.

The standard of care in Eastern centers, such as in Japan and Korea, consists of SG or TG with at least a D2 lymph node dissection, because a D1 dissection is considered an inadequate oncologic procedure. Because of their referral system, where patients with gastric cancer are evaluated by and operated on by foregut specialists, the reported perioperative morbidity and mortality of the standard D2 dissection is less than what was reported in the Dutch and MRC trials. More recent data generated from specialized Western centers compare more favorably with Eastern data, so it may be concluded that the learning

curve for performing a D2 gastrectomy may have been responsible for such disparate results from the 1990s.

As to whether more extensive lymph node dissection provides a survival benefit, Sasako and colleagues[44] evaluated the addition of para-aortic lymph node dissection (PAND) to D2 dissection. Between 1995 and 2001, patients with potentially curable T2b, T3, or T4 gastric adenocarcinoma were included, because para-aortic nodal involvement may only occur once the subserosa is invaded. Of 523 patients, 263 underwent standard D2 dissection whereas 259 underwent D2 dissection with PAND. Each treatment arm was well matched for extent of gastric resection and frequency of splenectomy and distal pancreatectomy. Patients who underwent PAND experienced longer operative times (300 minutes vs 237 minutes, $P<.001$), greater median blood loss (660 mL vs 430 mL, $P<.001$), and more transfusions (30.0% vs 14.1%, $P<.001$). Twenty-two of 259 patients (8.5%) who underwent PAND had positive lymph nodes. Morbidity was higher in the PAND group but did not achieve statistical significance (28.1% vs 20.9%, $P = .07$). Overall survival rates were similar between the standard D2 dissection and D2 dissection plus PAND (69.2% vs 70.3%), as were recurrence-free survival rates (62.6% vs 61.7%). Thus, the investigators could not recommend routine para-aortic node dissection as part of resection of potentially curable gastric malignancies.

POSITIVE MARGINS

Positive resection margins for potentially curative gastric cancer are associated with poorer outcomes. Shen and colleagues[45] retrospectively reviewed patients with primary tumors in the gastric cardia, Siewert type II or III, who had undergone TG with curative intent between 1995 and 2000. Frozen sections were not done, D2 dissection was performed, and adjuvant fluorouracil-based chemotherapy was administered except for tumor grade T2N0M0. Of 191 patients, 16 (8.4%) had positive margins at permanent section, 15 of whom were stage III or IV. Characteristics that were associated with positive margins included tumor size greater than 5 cm ($P = .001$), depth of tumor invasion ($P<.001$), node involvement ($P<.001$), and stage ($P<.001$). On multivariate analysis, only tumor stage was independently associated with survival ($P<.001$); positive margins were not associated ($P = .23$). Median survival in those with positive margins, however, was poorer (33.9 months vs 62.4 months, $P<.001$).

Cho and colleagues[46] also retrospectively reviewed the clinical impact of positive margin status. Between 1987 and 2001, 2740 consecutive patients presented for potentially curable advanced gastric cancer, defined as at least T2. All patients underwent intraoperative frozen section and D2 or D3 lymph node dissection. Positive margins were those that were positive on permanent section despite negative frozen section. Forty-nine patients (1.8%) had positive margins, of whom 1 underwent relaparotomy, 43 underwent chemotherapy, and 5 received no further treatment. Factors associated with positive resection margins included greater stomach involvement by the tumor ($P = .001$), signet ring morphology and poor differentiation ($P = .019$), TNM stage of IIIB or IV ($P = .001$), and tumor depth of T3 or T4 ($P = .001$). Five-year overall survival was poorer with positive margins (28% vs 51%, $P = .0028$). In the presence of positive lymph nodes, survival was similar between negative and positive margins (37 months vs 33 months, $P = .259$). In node-negative disease, however,

positive margins were associated with poorer 5-year survival (29% vs 80%, $P = .0001$). Sun and colleagues[47] performed a similar retrospective review from 1980 to 2006. Frozen section was performed if margins were considered insufficient, and reresection of margins was performed after positive frozen section. Of 2269 patients who underwent an intended R0 resection, 110 (4.8%) had a positive margin on permanent section. Positive margins were associated with worse outcomes for less invasive tumors (T1 or T2) ($P<.001$), limited nodal involvement (N0 or N1) ($P<.001$), and lower-stage malignancies (stage I or II) ($P = .006$). Although 5-year overall survival was worse with positive margins (25.8% vs 52.6%, $P<.001$), this association did not hold up on multivariate analysis. This indicates that negative margins are more important when resecting lower-stage tumors, because advanced tumors have likely progressed beyond the primary site.

PALLIATIVE SURGERY

Palliative surgery is defined as procedures that are performed with noncurative intent to improve quality of life or to relieve symptoms secondary to an advanced malignancy.[48] Worse outcomes after palliative surgery have been associated with poor functional status, recent weight loss, and low serum albumin. Appropriate selection of patients with advanced cancer of any type for palliative surgery can yield several months of symptom relief at the end of life while minimizing operative morbidity and mortality. Involvement of the patient, patient's family members, and operating surgeon in the palliative decision-making process, known as the palliative triangle, has been associated with more successful relief of symptoms and fewer postoperative complications.[49] The importance of explicitly defining procedures performed on patients with advanced gastric cancer as palliative has been emphasized by Miner and colleagues.[50] Among 307 patients who underwent R1 or R2 resection for noncurable disease, 147 (47.9%) underwent procedures that were performed with palliative intent whereas the remainder were nonpalliative. Patients undergoing palliative procedures more frequently had distal cancers, nodal involvement, and metastatic disease on staging. Perioperative morbidity (49% vs 61%, $P = .25$) and mortality (7% vs 4%, $P = .46$) were similar, but palliative patients had a lower rate of high-grade complications (22% vs 29%, $P = .049$), likely due to less extensive surgical procedures performed. Median overall survival was 10.6 months but was significantly decreased among palliative patients (8.3 months vs 13.5 months, $P<.001$).

The natural history of metastatic gastric cancer has been analyzed in terms of need for palliative intervention by Sarela and colleagues.[51] Between 1993 and 2002, 147 patients with metastatic disease diagnosed on staging laparoscopy and 18 patients with metastatic disease discovered on laparotomy after negative laparoscopy were included. Disease most commonly involved the peritoneum, with some patients with liver and/or distant lymph node involvement. All patients started single-agent or multiagent chemotherapy after diagnosis of metastatic disease. Of 97 patients who were treated only at the investigators' institution, 48 (49.5%) underwent palliative procedures; 29 had a procedure involving the GEJ or stomach, 7 had a procedure on a distant anatomic site, and 12 patients had a combination of the 2 types of surgery. Median overall survival was 10 months; however, median survival after any palliative procedure was 3 months. On multivariate analysis, survival was improved in patients with better baseline performance status and limited peritoneal metastasis. The

investigators argued that palliative procedures often did not improve survival and that preemptive palliative procedures before symptomatic presentation were not necessary.

The benefit of palliative resection for incurable gastric cancer has been debated (Table 3). These arguments are often limited by emphasis on survival data or morbidity and mortality rates rather than the more appropriate palliative endpoints of symptom resolution or potential quality-of-life benefits. Hartgrink and colleagues[52] compared exploratory laparotomy with or without surgical bypass to palliative gastric resection in unresectable patients identified in the prospective Dutch D1D2 trial. Of 285 patients with unresectable tumors (T^+), hepatic (H^+) or peritoneal (P^+) metastasis, or distal lymph node involvement (N^+), 156 (54.7%) underwent palliative resection. Median survival in resected patients was improved over those who had exploratory laparotomy with or without gastroenterostomy (8.1 months vs 5.4 months, $P<.001$); however, they had higher morbidity (38% vs 12%, $P<.001$) and length of stay (15 days vs 10 days, $P<.001$). Perioperative mortality was similar (12% vs 10%). The investigators concluded that patients under 70 years of age with only 1 of the 4 criteria for unresectability obtained a survival benefit from resection, whereas older patients or those with more than one manifestation of unresectable disease had no survival benefit. Samarasam and colleagues[53] retrospectively reviewed consecutive patients from 1999 to 2003 who underwent palliative surgery for gastric adenocarcinoma. Of 151 patients, 107 (70.9%) underwent either SG or TG if macroscopic free margins could be obtained; the remaining 44 underwent laparotomy with or without gastrojejunostomy. All patients received adjuvant chemotherapy. Resectability decreased with increasing number of criteria for unresectability (T^+, H^+, P^+, and N^+). Median survival was improved in resected patients (24 months vs 12 months, $P = .0003$); however, the survival benefit disappeared with more than one criterion for unresectability. Median survival was similar between SG and TG (24 months and 20 months, respectively). Saidi and colleagues[54] compared no resection with palliative resection for patients with stage IV gastric cancer between 1990 and 2000. Of 105 patients, 24 (22.9%) underwent palliative resection, whereas the remainder underwent laparotomy with or without bypass. Some patients received adjuvant chemotherapy. Mean survival was improved in the resected group (13.2 months vs 5.5 months, $P = .006$), mostly in the group who also received adjuvant chemotherapy. Huang and colleagues[55] compared outcomes of palliative gastrectomy to exploratory laparotomy with or without bypass in unresectable gastric cancer. From 1988 to 2008, 365 patients underwent palliative SG (71.5%) or TG (28.5%) and 151 patients underwent exploratory laparotomy with or without gastrojejunostomy. Median overall survival was improved in the resected group (10.2 months vs 4.5 months, $P<.001$), and it was similar between SG and TG (10.3 months vs 8.7 months, $P = .135$). Palliative resection was tolerated better in younger patients. Survival was improved in resected patients even with more than 1 criterion for unresectability having been met. Zhang and colleagues[56] compared outcomes of palliative TG with exploratory laparotomy with or without gastrojejunostomy or no surgery for advanced proximal malignancy. Of 377 patients undergoing surgery, 197 (52.3%) underwent TG, whereas 180 underwent laparotomy with (n = 78) or without (n = 102) bypass. Median survival was improved in the resected group (16.4 months vs 5.8 months gastrojejunostomy, 4.7 months laparotomy only, 5.5 months no surgery; $P<.05$). Based on these data, palliative gastric resection improves median survival, and modern surgical techniques have been able to

reduce perioperative morbidity and mortality to acceptable levels. This benefit is presumably due to reduction in overall tumor burden.

The apparent survival benefit from noncurative gastrectomy from these series is attributable to them being performed on patients without widely disseminated disease. Often, survival is worse in patients operated on with palliative intent compared with those who had noncurative nonpalliative resection. This highlights the importance of patient selection for palliative surgery, because increased survival is not a goal of treatment but rather durable symptom improvement. In an effort to more fully evaluate potential benefits from palliative surgery in gastric cancer, Miner and Karpeh[57] performed a partitioned survival analysis, which assesses state of health in relation to treatment, toxicity, and relapse over time. Patient health state was defined in terms of time without symptoms or toxicity (TWiST). Of 307 noncurative resections included in the analysis, 147 (48%) were performed with palliative intent. In the palliative subgroup, patients experienced an average of 8.5 months in the TWiST state. This time was significantly reduced due to high-grade complications, such as unplanned reintervention, ICU admission, or permanent disability (2.1 months, $P = .04$). In addition, patients with multiple sites of metastasis trended toward less time in the TWiST state (4.9 months, $P = .08$). These data demonstrates the importance of appropriate patient selection, indicating that perhaps the most symptomatic patients have the greatest potential benefit. Preoperative counseling is critical in defining treatment goals and minimizing unnecessary treatment toxicity.

Recently, endoscopic stent placement for malignant gastric outlet obstruction (GOO) has gained attention. Maetani and colleagues[58] retrospectively reviewed palliative stent placement versus gastrojejunostomy for GOO; 22 patients with gastric adenocarcinoma and GOO who underwent endoscopic stenting between 1994 and 2004 were compared with 22 contemporary patients who had undergone gastrojejunostomy. Exclusion criteria were prophylactic intervention and the indication for procedure being recurrent cancer. Morbidity was higher among the gastrojejunostomy group (18.2% vs 4.5%, $P = .20$) whereas median survival was similar (90 days vs 65 days, $P = .79$). The stent group, however, had faster return to diet (2 days vs 8 days, $P<.0001$) and shorter median length of stay (19 days vs 28 days, $P = .056$). In this underpowered study, the procedures seemed approximately equivalent in outcomes. Jeurnink and colleagues[59] conducted a multicenter, randomized trial to compare palliative stent placement to gastrojejunostomy for GOO. Between 2006 and 2008, 21 patients underwent stent placement and 18 patients underwent gastrojejunostomy for GOO secondary to various gastrointestinal malignancies, most commonly pancreatic. Despite early advantages in the stent group, such as return to diet (5 days vs 8 days, $P<.01$) and shorter length of stay (7 days vs 15 days, $P = .04$), stents more often had recurrent obstructive symptoms (23.8% vs 5.6%, $P = .02$) and need for reintervention (33.3% vs 11.1%, $P<.01$). In addition, quality of life was initially approximately equal but slightly improved at 5 months in the gastrojejunostomy group. Therefore, stenting is likely more beneficial for patients with a short life expectancy, whereas gastrojejunostomy more often provides durable symptom improvement. Kim and colleagues[60] compared covered and noncovered stents in a prospective, randomized study; 80 patients with gastric adenocarcinoma but no prior gastric surgery were enrolled between 2003 and 2007, 40 in

each group. Patency at 8 weeks was similar between covered and noncovered stents (61.3% vs 61.1%). Stent migration, detected by endoscopy, was increased in the covered stent group (25.8% vs 2.8%, *P* = .009), but restenosis from tumor in growth was decreased (0% vs 25.0%, *P* = .003). The investigators could not recommend one type of stent over the other due to their respective trade-offs.

NEOADJUVANT CHEMOTHERAPY

In recent years, much attention has been given to neoadjuvant chemotherapy as an adjunct to potentially curative gastric cancer surgery in an effort to improve outcomes. Hartgrink and colleagues[61] first presented results of a randomized trial to evaluate neoadjuvant administration of 5-fluorouracil, doxorubicin, and methotrexate (FAMTX) in potentially curable gastric cancer. Between 1993 and 1996, 56 eligible patients were enrolled in the study, 27 of whom received preoperative FAMTX. Due to poor enrollment, the study was terminated early. Subsequent analysis showed a lower overall 5-year survival rate in the FAMTX group (21% vs 34%, *P* = .17); this was more pronounced for those who underwent R0 resection (32% vs 53%, *P* = .07). The study was limited by the small sample size, which was an effect of unwillingness to proceed both on providers' and patients' parts. At the time of the study, FAMTX was the chemotherapy regimen of choice, but cisplatin-based regimens soon supplanted it. Cunningham and colleagues[62] were the first to report results of such a regimen in a randomized trial, known as the MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial, conducted between 1994 and 2002. Patients with potentially curable, at least stage II gastric and distal esophageal adenocarcinoma were randomized to surgery alone (n = 253) or neoadjuvant and adjuvant epirubicin, cisplatin, and 5-fluorouracil (n = 250). Of 209 patients who completed 3 cycles of preoperative chemotherapy and underwent surgery, only 137 (65.6%) began postoperative chemotherapy and only 104 (49.8%) completed all 3 cycles of postoperative chemotherapy. Five-year overall survival was improved in the chemotherapy group (36.3% vs 23.0%, *P* = .009) as was progression-free survival. The neoadjuvant portion was likely responsible for a good deal of the survival benefit seen in this study, because fewer than half of patients assigned to chemotherapy completed all 3 postoperative cycles, and other studies at the time failed to show significant benefit from adjuvant chemotherapy. Schuhmacher and colleagues[63] conducted a randomized trial of cisplatin, folinic acid, and 5-fluorouracil as neoadjuvant treatment. Patients with stages III or stage IV gastric or distal esophageal adenocarcinoma without distant metastasis were randomized to surgery alone (n = 72) or preoperative cisplatin, folinic acid, and 5-fluorouracil (n = 72) between 1999 and 2004. The study was terminated early due to poor enrollment. Of the 72 patients in the chemotherapy group, 70 underwent surgery, but only 45 completed both preoperative cycles of chemotherapy. Intraoperative R0 resection rates were considered equal, but pathology demonstrated an improvement in the chemotherapy group (81.9% vs 66.7%, *P* = .036). However, 5- year overall survival was similar (HR 0.84; 95% CI, 0.52–1.35; *P* = .466). The investigators attributed a lack of demonstrated survival benefit to poor study power, more extensive lymphadenectomy, overall higher tumor stage, and lower rates of completion of neoadjuvant therapy. A similar trial evaluating neoadjuvant 5-fluorouracil and cisplatin was performed by Ychou and colleagues.[64] Between 1995 and 2003, 219 patients who were

randomized to surgery alone (n = 110) or surgery with perioperative 5-fluorouracil and cisplatin (n = 109) were eligible for analysis. Some patients in each group underwent postoperative chemotherapy or radiotherapy. The chemotherapy group had improved 5-year overall survival (HR 0.69; 95% CI, 0.50–0.95; *P* = .02) and disease-free survival (HR 0.65; 95% CI, 0.48–0.89; *P* = .003); the overall survival rates were 38% versus 24%, respectively. Yoshikawa and colleagues[65] prospectively evaluated the effectiveness of neoadjuvant chemotherapy in gastric cancer with significant nodal involvement. Patients with gastric adenocarcinoma and bulky N2 disease and/or para-aortic nodal involvement but without more distant disease received preoperative irinotecan and cisplatin between 2000 and 2003. Fifty-patients were enrolled, of whom 41 received the full neoadjuvant course and then underwent radical gastrectomy. The trial was closed prematurely due to high treatment-related mortality (5%). The 3-year overall survival rate was 27%, however, which was better than expected for patients with significant nodal involvement. A prospective randomized phase II trial (COMPASS-D) comparing neoadjuvant S-1 and cisplatin versus S-1, cisplatin, and docetaxel has recently been proposed by Yoshikawa and colleagues.[66]

SUMMARY

Surgical resection remains the only potentially curative treatment of gastric cancer. Newer staging modalities aid in minimizing unnecessary laparotomy in noncurative disease. Adequate lymphadenectomy may improve outcomes, similar to selective resection of adjacent organs based on tumor invasion. Lymph node involvement and positive surgical margins are associated with poorer overall survival. Neoadjuvant chemotherapy may downstage responsive tumors and may improve survival even with extensive lymphatic disease. Palliative surgery for advanced gastric cancer remains important in providing symptom relief in appropriately selected patients.

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KEY POINTS

- Surgical resection remains the only potentially curative treatment of gastric cancer.
- Newer staging modalities aid in minimizing unnecessary laparotomy in noncurative disease.
- Adequate lymphadenectomy may improve outcomes, similar to selective resection of adjacent organs based on tumor invasion.
- Lymph node involvement and positive surgical margins are associated with poorer overall survival.
- Neoadjuvant chemotherapy may downstage responsive tumors and may improve survival even with extensive lymphatic disease.
- Palliative surgery for advanced gastric cancer remains important in providing symptom relief in appropriately selected patients.

Table 1

TNM staging classification, 7th edition; stages 0 to IIIC are M0

T Stage	N Stage	Stage
Tis: carcinoma in situ	N1: 1–2 nodes	Stage 0: TisN0
T1a: lamina propria T1b: submucosa	N2: 3–6 nodes	Stage IA: T1N0 Stage IB: T2N0, T1N1
T2: muscularis propria	N3a: 7–15 nodes N3b: >15 nodes	Stage IIA: T3N0, T2N1, T1N2 Stage IIB: T4aN0, T3N1, T2N2, T1N3
T3: subserosa		Stage IIIA: T4aN1, T3N2, T2N3 Stage IIIB: T4bN0, T4bN1, T4aN2, T3N3 Stage IIIC: T4bN2, T4bN3, T4aN3
T4a: perforates serosa T4b: invades adjacent structures		Stage IV: any T, any N, M1 Positive cytology is M1 disease

Table 2

Multiple organ resections in treatment of invasive gastric cancer

Author	Patients	Tumor Grade	30-Day Mortality	30-Day Morbidity	R0 Resection	5-Year Survival	R0 5-Year Survival	Recurrence Rate
Kobayashi et al,[24] 2004	82	T3, T4	1.2%	28%	50 (61.0%)	31.1%	36.9% (*P* = .004)	NR
Kunisaki et al,[25] 2006	117	T4	4.3%	22.2%	38 (32.5%)	16.0%	32.2% (*P*<.0001)	50%
Carboni et al,[26] 2005	65	T3, T4	1.5%	27.7%	40 (61.5%)	21.8%	30.6% (*P* = .001)	NR

Abbreviation NR, not reported.

Table 3

Survival benefit of palliative resection compared with laparotomy with or without bypass

Author	Number of Patients	Resected Patients	30-Day Mortality	30-Day Morbidity	Unresected Median Survival	Resected Median Survival
Hartgrink et al,[52] 2002	285	156 (54.7%)	12%	38%	5.4 mo	8.1 mo (*P*<.001)
Samarasam et al,[53] 2006	151	107 (70.9%)	NR	NR	12 mo	24 mo (*P* = .0003)
Saidi et al,[54] 2006	105	24 (22.9%)	8.3%	33.3%	5.5 mo (mean)	13.2 mo (mean) (*P* = .006)
Huang et al,[55] 2010	516	365 (70.7%)	3.3%	18%	4.5 mo	10.2 mo (P<.001)
Zhang et al,[56] 2011	377	197 (52.3%)	3.0%	24.3%	5.8 mo bypass 4.7 mo no bypass	16.4 mo (*P*<.05)

Abbreviation NR, not reported.