Multimodality Therapy of Localized Gastric Adenocarcinoma

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Abstract

Surgical resection is the primary method of obtaining a potential cure for patients with gastric adenocarcinoma. However, chemotherapy or chemoradiotherapy offer significant improvement in survival over surgery alone. Much of the difficulty in deciding the optimal treatment strategy is choosing between perioperative chemotherapy or adjuvant chemoradiotherapy. Adding to the complexity is the potential for incorporating treatment strategies based on clinical trials performed in Asia. There is likely a difference in tumor biology between Eastern and Western patients with gastric adenocarcinoma, in addition to the clear differences in screening, pathologic assessment, and surgical technique. Even among tumors in Western populations, heterogeneity of histology, anatomy, and staging among studies make cross-trial comparisons difficult. There is also active controversy surrounding the staging and management of gastroesophageal junction tumors. Lastly, the benefit of extended lymph node dissection is not clear based on the existing studies and has not been firmly established as a surgical standard of care for all patients. Future goals include better classification of gastric cancer, continued pursuit of randomized trials in Western populations, standardization of surgical technique, and incorporation of targeted therapies.

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Compare and contrast gastric cancer tumor biology, staging, surgical techniques and incorporation of adjuvant therapy between Eastern and Western clinical trial populations
- Summarize the need for a broad multidisciplinary approach to the management of patients with gastric cancer

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Multidisciplinary Approach

Although multimodality therapy in gastric cancer is primarily focused on surgical, medical, and radiation oncology, a broad multidisciplinary team approach, including conference attendance with radiologists, gastroenterologists, and pathologists, is needed to determine the optimal staging and treatment approach.¹ This approach facilitates a multidisciplinary discussion that incorporates clinicians who would otherwise not be directly involved, and therefore goes beyond simple referral for multidisciplinary clinical evaluation. This approach is not emphasized in regions of the world where a surgery-first approach is standard of care, radiation therapy is infrequently used, and many cancers are found at an early stage and don't require adjuvant chemotherapy.

Worldwide, gastric cancer is the third leading cause of death in men and the fifth leading cause of death in women.² Gastric cancer incidence rates are highest in Eastern Asia, Central and Eastern Europe, and South America, whereas rates are low in Northern America. One of the first decision points in analyzing the existing studies on gastric cancer and deciding on the optimal treatment approach is whether gastric cancer is the same in Eastern and Western populations. In regard to gastric cancer epidemiology for this review, Eastern studies will be defined as trials from Japan, South Korea, Taiwan, and China. Western populations will be defined as the United States and Western Europe. There are few trials from South America, and further research is needed to determine whether survival for patients from South America is similar to that for Eastern or Western populations.

The difference in incidence rates is partly attributed to differences in food preservation techniques, regional dietary preferences, and *Helicobacter pylori* infection rates. Regional differences in incidence support variations in tumor biology that raise concern over using Eastern treatment strategies in Western populations. Western patients with gastric cancer are also older and have a higher frequency of several adverse prognostic factors, such as proximal tumor location, poorly differentiated histology, and the presence of signet ring cells.

In addition to the clear differences in tumor biology and histology, there are also differences in the stage at presentation (primarily due to widespread screening in Japan and South Korea), surgical technique, and adjuvant therapy. Because of these differences, it is difficult to compare patients between

regions based on stage and to fully adjust for differences in staging and treatment. Investigators have explored this challenging research question, reporting a better survival rate for Eastern than Western patients on adjusted analysis, although there are significant differences even among Eastern countries, and meaningful comparison will likely require more than multivariable statistical analysis.³⁻⁵ Current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gastric Cancer are primarily based on Western studies, and we will highlight recommendations with regional implications regarding systemic therapy or surgery herein.¹ Table 1 highlights the differences in the various trials that will be covered in this review, stratified by whether the trial was performed in Eastern or Western populations of patients with gastric cancer.

Staging for Localized Gastric Cancer

A chest/abdominal/pelvic CT scan is currently the mainstay for imaging for resectable gastric adenocarcinoma. PET/CT imaging is also recommended if clinically indicated in patients without evidence of metastatic disease on routine CT imaging, although this recommendation requires further support.¹ Gastric adenocarcinoma, particularly diffuse type, signet ring cell type, or tumors with mucinous histology, may not demonstrate increased uptake on PET/CT imaging, and conflicting results have been reported on the association between increased initial standardized uptake value and improved survival in patients receiving preoperative therapy.⁶⁻⁸

Diagnostic laparoscopy with cytology is an important consideration for patients with potentially resectable cancer, because approximately 30% of patients will have radiologically occult carcinomatosis or positive cytology.^{1,9} In addition to the benefit of avoiding laparotomy, patients with low-volume peritoneal disease have the potential for relatively long overall survival and should be considered for trials aimed at improving what has historically been reported as dismal survival.^{10,11}

Many patients will present for initial oncologic evaluation with only a diagnostic endoscopy report that is inadequate for multimodality recommendations. Repeat endoscopy with endoscopic ultrasound can be crucial in determining the anatomic location of the tumor and the proximity to the gastroesophagus.

Table 1. Overall Survival Rates for Trials of Resectable Gastric Cancer From Western and Eastern Centers

Trial	Outcome	Surgery Alone	Chemotherapy	Chemoradiotherapy
Western centers				
Intergroup 0116 ¹⁸	3-y OS	41%		50%
MAGIC ¹²	5-y OS	23%	36%	
FNCLCC ¹³	5-y OS	24%	38%	
CROSS ²⁰	5-y OS	34%		47%
Eastern centers				
ACTS-GC ⁴¹	5-y OS	61%	72%	
CLASSIC ¹⁶	3-y OS	78%	83%	
ARTIST ¹⁷	5-y OS		73%	75%

Abbreviation: OS, overall survival.

geal junction (GEJ). Although lesions amenable to endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) are rare in the United States, lesions amenable to such techniques include nodules 2 cm or less, well- or moderately well-differentiated, without involvement beyond the superficial submucosa, and with clear margins.¹ These guidelines exclude most cancers diagnosed in the West, and consideration must be given to local expertise in not only the endoscopic resection but also the quality of the ultrasound documenting an early lesion.

Chemotherapy for Localized Gastric Cancer

Perioperative Chemotherapy

There are preoperative and postoperative choices for administering chemotherapy to patients with potentially resectable gastric cancer. Preoperative chemotherapy, as part of a planned perioperative approach, is based on the MAGIC trial in which patients received epirubicin, cisplatin, and infusional FU for 3 cycles preoperatively and postoperatively compared with surgery alone.¹² The 5-year survival rates were 36% in the perioperative chemotherapy arm versus 23% in the surgery alone arm, despite only 42% of patients randomized to perioperative chemotherapy completing all 6 cycles. There was also variability in surgical technique, with only 40% of patients having undergone a D2 lymph node dissection. Notably, there was not a significant difference in postoperative complications, providing support to the concept that preoperative therapy does not increase surgical

risk. Variability in tumor location was also present, with approximately 25% of patients having lower esophageal or GEJ tumors.

Further support for perioperative therapy is found in the French FNCLCC/FFCD trial, in which patients with distal esophageal (n=25), gastroesophageal (n=144), and gastric (n=55) adenocarcinoma were randomized to perioperative therapy with 5-FU and cisplatin versus surgery alone.¹³ Similar to the MAGIC trial, 5-year overall survival was higher in the perioperative therapy group (38%) compared with the surgery-alone group (24%).¹³ Another similarity to the MAGIC trial is that only approximately half of the patients were able to receive postoperative chemotherapy, as outlined in Figure 1.

Postoperative Chemotherapy

Studies of postoperative chemotherapy alone are more conflicting and the optimal regimen is less clear. Because of the number of studies of postoperative

Figure 1. Completion rates for treatment arms in randomized controlled trials of surgery with chemotherapy or chemoradiotherapy versus surgery alone in patients with gastric or gastroesophageal cancer.

chemotherapy compared with surgery alone in gastric cancer, authors have used meta-analyses to help clarify this area of controversy. Although reviews that included Eastern trials tend to show a benefit for postoperative chemotherapy, studies limited to Western populations suggest less benefit.^{14,15} Current NCCN Guidelines for Gastric Cancer include postoperative chemotherapy (capecitabine with oxaliplatin or cisplatin) for patients who have undergone a D2 lymph node dissection based on the CLASSIC and ARTIST trials.^{1,16,17} In the CLASSIC trial, patients in South Korea, China, and Taiwan who had undergone gastrectomy were then randomized to capecitabine plus oxaliplatin for 8 cycles versus no postoperative therapy. Five-year overall survival was higher in patients who received postoperative chemotherapy (78% vs 69%).¹⁶ The ARTIST trial compared postoperative chemotherapy (capecitabine and cisplatin) versus postoperative chemotherapy followed by chemoradiotherapy (capecitabine with 45 Gy); results showed no difference in overall survival.¹⁷

Chemoradiotherapy for Localized Gastric Cancer

Similar to chemotherapy, there are also preoperative and postoperative choices for the application of chemoradiotherapy in localized gastric cancer. Current recommendations for postoperative chemoradiotherapy are primarily based on the Intergroup 116 trial, a US study in which patients received one cycle of FU/leucovorin, then FU/leucovorin with 45 Gy, followed by 2 more cycles of FU/leucovorin compared with surgery alone.¹⁸ Three-year overall survival rates were higher in patients treated with chemoradiotherapy (50%) compared with surgery alone (41%). The most recent analysis continues to demonstrate a survival benefit for adjuvant chemoradiotherapy, with 24% more patients in the treatment arm disease free compared with the surgery alone arm.¹⁹ The ARTIST trial from South Korea failed to show a benefit for postoperative chemoradiotherapy compared with chemotherapy; however, subset analysis demonstrated an improvement in 3-year disease-free survival (DFS) associated with chemoradiotherapy in patients with node-positive disease (76% vs 72% with chemotherapy) and intestinal type tumors (94% vs 83% with chemotherapy).¹⁷ Therefore, the

authors have initiated a new trial (ARTIST 2; ClinicalTrials.gov identifier: NCT01761461) focusing on patients with node-positive, D2-resected gastric cancer, which is currently active.

Preoperative chemoradiotherapy is also included in current guidelines, based on a randomized controlled trial in patients with distal esophageal and gastroesophageal cancer. In the CROSS trial, patients randomized to chemoradiotherapy followed by surgery showed an improvement in 5-year overall survival (47%) compared with those treated with surgery alone (34%).²⁰ It should be noted that only 24% of the patients had GEJ tumors and 23% had squamous cell carcinoma histology. Patients in this study underwent either a transthoracic resection with 2-field lymph node dissection or transhiatal resection, with gastric tube reconstruction with a cervical anastomosis, demonstrating that this study may have limited application in patients with gastric cancer.²⁰ However, there are several phase II trials of preoperative induction chemotherapy and chemoradiotherapy that demonstrate this approach is feasible with good response rates, R0 resection rates, and survival.^{21–23} It should be noted that there are no randomized trials of preoperative chemoradiation therapy for gastric cancer that does not involve the GEJ, and current NCCN recommendations are limited to category 2B for these types of lesions.

In another phase III study, the POET trial from Germany, patients with locally advanced cancer of the lower esophagus and GEJ were randomized to either chemotherapy followed by surgery versus chemotherapy followed by chemoradiation followed by surgery.²⁴ The study was closed early due to low accrual, with only a nonsignificant trend noted toward improved survival in the patients treated with preoperative chemoradiation therapy. However, there were significantly higher pathologic complete response rates and tumor-free lymph node rates found in the patients treated with preoperative chemoradiation.

The CRITICS trial essentially compared the MAGIC regimen of perioperative chemotherapy to preoperative chemotherapy plus an Intergroup 116 approach of postoperative chemoradiotherapy. Recently presented at the 2016 ASCO Annual Meeting, the results of this trial showed that 5-year overall survival did not differ between the 2 arms (41% in both).²⁵ The authors noted that only approximately 50% of patients completed the full treatment, again

raising questions about the need to administer therapy preoperatively. Figure 1 displays the reported completion rates for the treatment arms of randomized trials comparing surgery alone versus surgery with chemotherapy or chemoradiotherapy.

Surgery for Localized Gastric Cancer

Patients medically fit for surgery with T1 lesions not amenable to EMR or ESD should be treated with upfront surgery. This practice is dependent on reliable endoscopic ultrasound, and consideration should be given to D2 lymphadenectomy due to the potential for upstaging on postoperative pathology. D1 lymphadenectomy includes the regional nodes along the lesser and greater curve and peripyloric area. D2 dissection includes D1 nodes and also all of the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery.¹

Extent of lymphadenectomy has been well studied in both Eastern and Western populations. The Eastern studies reliably justify D2 dissection as the standard of care, whereas Western studies are less clear. Historical trials of extended lymphadenectomy in Western populations include the MRC trial and the Dutch trial,^{26,27} which failed to show a benefit with extended lymphadenectomy, attributed to the high perioperative morbidity (43%–46%) and mortality (10%–14%) associated with pancreatectomy and splenectomy.^{26–29} The Italian IGCSG-R01 trial demonstrated a low mortality and morbidity with D2 lymphadenectomy when routine pancreatectomy and splenectomy was avoided. This trial also failed to show a difference in survival on long-term follow-up, which may be related to the relatively small difference in the median of retrieved lymph nodes for patients with D1 (N=25) and D2 (N=33) lymphadenectomy, the rate of contamination in the D1 group (18%), and noncompliance in the D2 group (34%).³⁰ In addition, one-third of the patients had pathologic T1 lesions and more than 40% had N0 disease.³⁰

Conversely, the long-term results of the Dutch trial showed an improvement in cancer-related mortality and locoregional recurrence in the D2 group.³¹ In addition, on subgroup analysis of the Italian trial, a benefit for extended lymphadenectomy was identified in patients with locally advanced gastric cancer and positive lymph nodes.³⁰ Expert centers also show a low risk associated with

D2 lymphadenectomy, and report an independent association with improved survival.^{32,33} Therefore, gastric cancer guidelines from Italy, Germany, Britain, ESMO/European Society of Surgical Oncology/European Society for Radiotherapy & Oncology, and NCCN continue to recommend extended lymphadenectomy.^{1,34–37}

The appropriate surgical approach for GEJ cancer is also defined, but requires flexibility in its application, particularly for patients with advanced tumors. Current AJCC staging classifies the pathologic stage of any patient with GEJ involvement and up to 5 cm of gastric involvement according to esophageal cancer criteria.^{38,39} Pathologic staging differs from treatment recommendations, however, because the Siewert classification is used to help determine whether to use a gastric or esophageal cancer surgical approach for tumors involving the GEJ. In short, the tumor center in a Siewert I lesion is more than 1 cm above the GEJ, between 1 cm above and 2 cm below the GEJ for Siewert II lesions, and more than 2 cm below the GEJ for a type III lesion.⁴⁰ Current recommendations suggest treatment according to esophageal guidelines for a type I and II lesion and gastric guidelines for a type III lesion.¹ In clinical practice, and particularly in Western populations with advanced gastroesophageal cancers that involve a considerable portion of the stomach, a combined approach with both a thoracic surgery and a surgical oncology team is helpful to obtain a margin negative resection. Recent studies support this approach for Siewert II lesions.³³

Summary

There is anatomic, histologic, and surgical heterogeneity in the current trials of chemotherapy and chemoradiotherapy in gastric cancer, and it may not be appropriate to apply treatment recommendations from trials in Eastern populations to patients with gastric cancer in the United States. However, there are high-quality trials to support the current guidelines for the treatment of patients with gastric cancer that include perioperative chemotherapy, postoperative chemoradiation therapy, preoperative chemoradiation therapy, and postoperative chemotherapy. Additional research is needed to help define the optimal approach to tumors of the GEJ and also to clarify the benefit of extended lymphadenectomy.

Future studies to identify which patients respond to preoperative treatment are needed to better allocate patients to the various approaches to chemotherapy and chemoradiotherapy.

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Multimodality Therapy for Gastric Cancer

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Posttest Questions

1. True or False: Perioperative chemotherapy is associated improved overall survival compared with surgery alone in patients with potentially resectable gastric cancer.
2. The current recommendations for postoperative chemoradiotherapy are primarily based on the _____ trial, although preoperative chemoradiotherapy is based primarily

- on the _____ trial.
- a. CLASSIC; ARTIST
 - b. Intergroup 116; CROSS
 - c. CRITICS; ARTIST 2
4. True or False: Patients medically fit for surgery with T1 lesions, not amenable to EMR or ESD, should be treated with upfront surgery.