ACR Appropriateness Criteria® Resectable Stomach Cancer

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For resectable gastric cancer, perioperative chemotherapy or adjuvant chemoradiation with chemotherapy are standards of care. The decision making for adjuvant therapeutic management can depend on the stage of the cancer, lymph node positivity, and extent of surgical resection.

Summary of Literature Review

Introduction/Background

In 2013, it was estimated that approximately 21,600 new cases of gastric cancer would occur in the United States, with an estimated 10,990 deaths from the disease.[1] Although 2000–2009 data demonstrated that gastric cancer is among the top four cancers with the largest annual decline in death rates in the United States,[1] it remains the second leading cause of death worldwide, with an annual estimated 989,600 new cases; the highest incidences are in Eastern Asia, Europe, and South America.[2] Although surgery remains the mainstay of management in gastric cancer, due to the high rate of locoregional and distant relapse, curative treatment generally requires a multimodality approach. Outcomes data from the Surveillance, Epidemiology, and End Results (SEER) program demonstrate an overall 5-year survival of approximately 30%, largely due to the fact that most patients present with locally advanced disease.[3] Although the 5-year survival for patients with localized disease at diagnosis is 62.3%, patients with lymph node–positive disease (27.7%) or metastatic disease (3.7%) have a much worse prognosis.[3]

Previously, the classification of gastric carcinomas included tumors arising at the gastroesophageal junction (GEJ) or tumors originating in the stomach at 5 cm or less from and crossing the GEJ. However, the seventh edition of the American Joint Committee on Cancer (AJCC) staging system defines gastric carcinomas as either tumors arising in the distal stomach or those originating in the proximal 5 cm of the stomach, but not crossing the GEJ.[4] This revision is mainly due to the prognostic implication of inappropriately including GEJ tumors in gastric tumor staging, since the outcomes for GEJ tumors after resection differ from the outcomes for gastric cancers.[5]

Prognostic Factors

Histologic tumor type can correlate with prognosis. The diffuse type/signet cell histology correlates with poorer outcomes, with a predilection for in intraperitoneal metastases when compared with the intestinal type.[6,7] Disease location also has a prognostic implication, and generally, outcomes are worse for proximal tumors of the cardia compared with distal gastric lesions.[8,9] Distal gastric tumors are more common in Asia and tend to have a more favorable 5-year overall survival rate of up to 60%, compared with gastric cardia tumors, which are more common in the United States, with 5-year overall survival rates of approximately 20%.[9,10] Although this difference in outcome may be due to genetic variations between the two populations, it may also be associated with the presence of widespread screening programs in countries such as Japan, which permit earlier detection of gastric cancer.[9] In addition, it is believed that the superior outcomes in Asia may be due to an increased utilization of more comprehensive yet potentially morbid D2 lymph node dissections, which remove additional lymph node basins, as compared with D1 nodal dissections, which only evaluate the perigastric nodal regions.[11] Although several studies have shown no survival advantage for a D2 resection, a recent study demonstrated a significant benefit in cancer specific–survival in long-term follow-up.[12-14]
Treatment

Breast conservation approaches

Surgical resection is an essential component of the management of gastric cancer and may involve various approaches, including endoscopic mucosal resection for early-stage disease (Tis, T1a) and minimally invasive laparoscopic resection or open gastrectomy for more advanced disease.[15]Minimally invasive approaches are becoming increasingly popular due to technological advances and the publication of data from randomized studies, which have demonstrated equivalent outcomes for laparoscopic procedures compared with open techniques.[15,16] Commonly, a total gastrectomy is utilized for proximal or middle-third lesions, and a partial gastrectomy is recommended for lesions in the distal third of the stomach.[15] The goal of resection is to obtain a negative margin (R0) resection, since a microscopically positive (R1) resection is associated with a worse prognosis; typically, a wide resection margin (4 to 6 cm) around the primary gastric cancer is desired for potentially curative surgery. Due to the propensity for mucosal spread, "simple" or "close" gross negative margins are not sufficient.[15] Given the significant disease-specific survival benefit with a more comprehensive nodal resection, a D2 nodal dissection with a minimum of 15 lymph nodes is preferred in large-volume centers.[14,17] The number of involved nodes reflects the burden of disease, and AJCC stage group survival estimates are thought to be best represented when at least 15 nodes are examined.[17] However, the concept of lymph node ratio, described as the ratio of positive lymph nodes to total number of retrieved lymph nodes, has been recently proposed as a more accurate indicator of lymph node metastasis. Based on several studies, use of lymph node ratio offers an independent prognostic factor that can reduce the influence of the extent of lymphadenectomy.[18]

Chemotherapy

In an autopsy-based series used to examine patterns of relapse, 80% to 93% of patients showed locoregional relapse after resection, with 49% demonstrating distant relapse.[15] Considering the high local and distant relapse rates with surgery alone, multiple studies have focused on efforts to improve outcomes with adjuvant treatment. Although initial studies did not seem to indicate a benefit to adjuvant chemotherapy over surgery alone for resectable stage II/III gastric cancer, two large randomized Asian trials (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer [ACTS-GC] and the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer [CLASSIC] trial) demonstrated a significant survival benefit with postoperative chemotherapy after D2 resection.[19,20] Although the benefit of postoperative chemotherapy has been questioned in patients treated with D1 gastrectomy in Western countries, the recent Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) meta-analysis of 17 worldwide randomized trials of postoperative chemotherapy vs surgery alone demonstrated a significant improvement in both overall survival and disease-free survival, as well as a significant improvement in median survival (4.9 years with surgery alone vs 7.8 years with the use of adjuvant fluoruracil [5-FU]-based chemotherapy).[21]

Studies have investigated the role of preoperative chemotherapy in gastric cancer. The Medical Research Council (MRC) Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial was a phase III design that randomized 503 patients with locally advanced, resectable adenocarcinoma of the stomach (74%), GEJ (14%), or distal esophagus (12%) to perioperative chemotherapy (epirubicin, cisplatin, and 5-FU [ECF]) vs surgery alone.[22] Although none of the patients in the chemotherapy group demonstrated a pathologic complete response, the 5-year overall survival rate was significantly improved with perioperative chemotherapy (36%) compared with surgery alone (23%), with no difference in postoperative morbidity between the two groups. However, the relative contribution of preoperative and postoperative chemotherapy in the study is unclear, since only 42% of patients assigned to perioperative chemotherapy completed protocol therapy and 34% of patients completing preoperative chemotherapy and surgery did not receive postoperative chemotherapy.[22] A smaller phase III trial including 224 patients with esophageal (13%), GEJ (62%), or gastric (25%) cancer noted a benefit in R0 resection rate and disease-free and overall survival using a perioperative platinum/fluorinated pyrimidine combination[23] (see Variant 1).

The European Organisation for Research and Treatment of Cancer (EORTC) conducted a study comparing preoperative chemotherapy (cisplatin and 5-FU) followed by surgery vs surgery alone. The results showed a significant improvement in the R0 resection rate (82% vs 67%) and a 7.1% rate of pathologic complete response, but failed to demonstrate an overall survival benefit.[24]
discrepancy in outcomes of the MAGIC and the EORTC studies may be attributed to differences between the two studies, including earlier-stage disease, higher statistical power, and postoperative chemotherapy in the MAGIC trial. In addition, patients in the EORTC trial were possibly more accurately staged with endoscopic ultrasound (EUS), whereas the MAGIC trial did not routinely utilize EUS-based staging.

**Radiation therapy**

Many studies have examined the role of radiation therapy (RT), both in the preoperative and postoperative setting, in efforts to achieve a benefit over surgery alone. Of these, a randomized controlled trial by the British Stomach Cancer Group examined the benefit of postoperative RT or postoperative chemotherapy compared with surgery alone. Although there was a significant reduction in locoregional recurrence with postoperative RT (10% with RT vs 27% with surgery alone), there was no benefit in survival with either adjuvant treatment.[25] The role of preoperative RT was evaluated in a large randomized trial from China that found that its addition to surgery vs surgery alone led to a significant improvement in overall survival (30% vs 20%), with benefits in local recurrence (39% vs 52%), reduction in regional nodal metastases, and tumor downstaging, as well as a higher resection rate (89.5% vs 79%).[26]

A recent meta-analysis of nine trials was conducted to examine the benefit of RT (postoperative, preoperative, or intraoperative) compared with surgery alone or surgery and chemotherapy. Results indicated a significant benefit in 5-year overall survival (relative risk, 1.39 by intent-to-treat analysis) with the addition of preoperative RT.[27] Of note, the meta-analysis included trials utilizing preoperative RT both alone and in combination with chemotherapy, making it difficult to distinguish the relative benefit of preoperative RT alone in this setting. The Quality Research in Radiation Oncology (QRRO) patterns of care survey noted that 19% of patients receiving RT as a component of treatment for stage IB–IV (nonmetastatic) gastric cancer did so in the preoperative setting.[28]

**Combined-Modality Treatment**

**Definitive chemoradiotherapy**

The majority of phase III studies for unresectable gastric cancer showed an advantage for combined-modality treatment over either RT or chemotherapy alone. Of these studies, Moertel et al[29] showed a significant improvement in 5-year survival, from 0% with RT alone (35–37.5 Gy) to 12% with 5-FU chemoradiotherapy for locally advanced gastric cancer without surgery. The Gastrointestinal Tumor Study Group compared combination chemotherapy with 5-FU and lomustine vs chemoradiotherapy with 5-FU and 50 Gy split-course RT, followed by maintenance chemotherapy, and found a significant benefit in 4-year survival (18% vs 7%) with chemoradiotherapy[30] (see Variant 2).

**Preoperative chemoradiotherapy**

The Radiation Therapy Oncology Group (RTOG) conducted a phase II study known as RTOG 9904 that investigated the benefit of preoperative chemoradiotherapy consisting of induction chemotherapy (leucovorin, 5-FU, and cisplatin) followed by 45 Gy of RT with concurrent chemotherapy (5-FU and paclitaxel). The results demonstrated a 26% pathologic complete response rate and a 77% R0 resection rate.[31] Walsh et al[32] conducted a randomized study of surgery alone vs neoadjuvant concurrent chemoradiotherapy (5-FU and cisplatin plus 40-Gy RT) followed by surgery in patients mainly with esophageal adenocarcinoma (65%), but including a proportion of patients with adenocarcinoma of the gastric cardia (35%). Results indicated that preoperative chemoradiotherapy resulted in a statistically significant improvement in median survival (16 months vs 11 months) and overall survival rates (32% vs 6%) over surgery alone. There have been several other promising small prospective trials examining the role of preoperative chemoradiotherapy.[33,34] It is important to note that one of the major benefits of the preoperative approach may be in the ability to select patients who might develop metastases and are therefore spared the morbidity of surgery, considering that approximately 12% to 17% of patients in prospective trials developed distant disease during preoperative chemoradiotherapy.[35] In addition, this approach has the potential benefit of improved adherence to treatment (see Variant 3).

**Postoperative chemoradiotherapy**

Among the initial studies demonstrating a benefit for adjuvant chemoradiotherapy in patients with
locally advanced gastric cancer, Moertel et al[36] randomized patients to surgery alone vs surgery plus adjuvant RT (37.5 Gy) concurrent with 5-FU chemotherapy. The results of the trial demonstrated a significant improvement in 5-year overall survival (23% vs 4%) with postoperative chemoradiotherapy. The landmark phase III Intergroup 0116 trial by Macdonald et al[37] examined the benefit of postoperative chemoradiotherapy in resectable gastric cancer and lower GEJ tumors (20%). This study included patients with stage IB–IV disease (according to AJCC 1988, 3rd ed.) randomized to surgery alone vs surgery followed by adjuvant chemoradiotherapy with 5-FU and leucovorin. The study demonstrated a significant benefit with adjuvant chemoradiotherapy, with an improvement in median survival (36 months vs 27 months) and 3-year overall survival rates (50% vs 41%). A recent 10-year update of the Intergroup 0116 study demonstrated unchanged significance for the benefits of both overall survival (hazard ratio [HR], 1.32) and progression-free survival (HR, 1.52) with postoperative chemoradiotherapy, in addition to a significant improvement in locoregional recurrence with adjuvant chemoradiotherapy (24%) compared with surgery alone (47%)[38] (see Variant 4). The Eastern Cooperative Oncology Group (ECOG) E7296 phase II trial of 3 cycles of preoperative paclitaxel and cisplatin plus adjuvant RT (45 Gy) with concurrent and postoperative 5-FU and leucovorin included 38 patients, 42% of whom had gastric tumors and 58% of whom had GEJ tumors. This regimen was difficult to tolerate; only 8% of patients were able to receive all assigned treatment and 66% had grade 3/4 toxicity. This regimen was not recommended to undergo further development.[39]

Only 10% of patients in the Intergroup 0116 trial had a D2 resection, suggesting that the benefit of adjuvant chemoradiotherapy may possibly be limited to cases with less extensive lymph node dissections. Dikken et al[40] performed an analysis of phase I/II trials that utilized adjuvant chemoradiotherapy, as well as studies from the Dutch Gastric Cancer Group Trial that randomized patients to D1 or D2 surgery alone. The analysis demonstrated that although chemoradiotherapy resulted in an overall significant decrease in local recurrence as compared with surgery alone (17% for surgery alone vs 5% for chemoradiotherapy), on subgroup analysis the local recurrence benefit of chemoradiotherapy was limited to D1 resected patients (8% with D1 surgery alone vs 2% with D1 plus chemoradiotherapy), with no improvement in local recurrence with the addition of postoperative chemoradiotherapy after D2 resection.[40] In contrast, Kim et al[41] conducted a study supporting the benefit of adjuvant chemoradiotherapy following D2 lymphadenectomy, showing a significant benefit in overall survival and progression-free survival for adjuvant chemoradiotherapy compared with surgery alone in patients undergoing D2 resection. The Adjuvant Chemoradiation Therapy in Stomach Cancer trial (ARTIST) examined the role of adjuvant treatment in patients with D2 resection followed by postoperative chemotherapy (cisplatin and capecitabine) or chemoradiotherapy, with the results demonstrating no benefit in disease-free survival with the addition of RT. However, a subgroup analysis revealed a significant improvement in patients with lymph node-positive disease, highlighting a role for postoperative chemomotherapy in D2 resected patients with node-positive disease[42] (see Variant 5).

Based on the previously mentioned data, resectable gastric cancer treatment may include lymph node resection followed by postoperative chemoradiotherapy with 5-FU and leucovorin chemotherapy (or infusional 5-FU or capecitabine) concurrently with 45-Gy external beam RT. Alternatively, perioperative chemotherapy as per the MAGIC trial can be considered in the management of gastric cancer.[43] For resected cases with positive or close margins, adjuvant chemoradiation should be employed.

**Radiation Therapy Technique**

The Intergroup 0116 trial utilized external beam RT with at least 4 MV photons, in a conventional anteroposterior/posteroanterior (AP/PA) field arrangement. Although the results of the trial contributed to the current standard of care, chemoradiotherapy treatment resulted in significant grade 3 or higher treatment-related morbidity, with 54% and 33% of patients experiencing hematologic and gastrointestinal toxicity, respectively.[37] With advances in technology and techniques for conformal radiation delivery, such as intensity-modulated radiation therapy (IMRT), it has become possible to attempt to spare normal tissue in an effort to decrease treatment-related toxicity. Several studies have investigated the possible advantage of IMRT in the treatment of gastric cancer. Ringash et al[44] compared three-dimensional conformal radiation therapy (3D-CRT) with IMRT planning in 20 patients. Evaluation of plans demonstrated improved target volume coverage with IMRT in 86% of cases, in addition to improved sparing of the spinal cord (74%), kidneys (69%), liver (71%), and heart (69%). Minn et al,[45] from Stanford University, suggested better preservation
of kidney function with significantly lower median post-radiation serum creatinine levels with IMRT compared with 3D-CRT. However, dosimetric evaluation of the kidneys showed nonsignificant improvements in the V20 but higher mean doses to the kidneys with IMRT. A recent study from MD Anderson Cancer Center that utilized preoperative IMRT concurrent with chemotherapy demonstrated excellent target coverage and organ sparing with IMRT but failed to demonstrate a significant difference in rates of acute toxicity, hospitalization, or feeding tube use compared with a group of patients treated with 3D-CRT.[46] Although IMRT may lead to improved organ sparing, currently there is insufficient clinical evidence regarding its role in decreasing treatment-related toxicity compared with 3D-CRT.

A survey of practice patterns by the QRRO attempted to analyze the penetration of multiple clinical performance measures and use of modern treatment planning approaches as a partial surrogate for quality. The three clinical performance measures included the following: use of CT-based treatment planning, generation of dose-volume histograms (DVH) to specifically evaluate dose to the kidneys and liver, and timely completion of prescribed postoperative RT. Of the institutions surveyed over a 24-month time period within the last decade (2005–2007), almost all postoperative gastric cancer patients received CT-based treatment planning, 75% underwent kidney DVH analysis, and nearly the same percentage completed RT as prescribed. The QRRO survey also showed that IMRT and image-guided RT were used in nearly one-fifth of patients.[28]

Ongoing Studies

Current data support a role for both combined-modality treatment with postoperative chemoradiotherapy and perioperative chemotherapy in resectable gastric cancer, based on the results of the Intergroup 0116 and MAGIC trials, respectively. Current studies are underway to further define the role of chemotherapy and RT in the management of gastric cancer. In the Dutch multicenter phase III CRITICS trial, patients are treated with 3 cycles of chemotherapy (epirubicin, cisplatin, and capecitabine) followed by surgery and randomization to 3 additional cycles of the same chemotherapy vs concurrent chemoradiotherapy (45-Gy RT, cisplatin and capecitabine). The randomized phase III MAGIC-B study will examine the benefit of the addition of the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab to the original perioperative MAGIC regimen. The ARTIST-2 trial will study the role of D2 lymphadenectomy alone vs D2 lymphadenectomy followed by chemoradiotherapy in patients with pathologically involved lymph nodes. Currently in active accrual, the phase II/III international Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR) will examine the role of neoadjuvant chemoradiotherapy (45-Gy RT, concurrent 5-FU or capecitabine) compared with neoadjuvant chemotherapy (ECF) for resectable disease, to determine any improvement in the endpoints of pathologic complete response and overall survival. The results of these studies and future trials will further delineate optimal management of gastric cancer in an effort to improve outcomes in this disease.

Summary of Recommendations

- After gastric cancer resection, adjuvant chemotherapy combined with chemoradiation (Intergroup 0116) are standard treatments and should be considered, particularly for D0 lymph node dissection, positive regional lymph nodes, poor clinical response to induction chemotherapy, or positive margins.
- A standard treatment option for resectable gastric cancer is perioperative chemotherapy, with 3 cycles of ECF (or other appropriate alternatives) given before and after surgery.
- For patients who have undergone D2 lymph node dissection, especially those with negative regional lymph nodes, adjuvant chemotherapy alone could be considered.
- Induction chemotherapy followed by surgery is a less studied treatment option. Few data exist comparing preoperative chemotherapy alone vs preoperative chemoradiation regimens with surgery for gastric cancer.
- For unresectable gastric cancer, standard treatment options include chemoradiation, preferably for the patient who can tolerate such a regimen. Alternatively, RT alone or chemotherapy alone is a viable treatment option for a patient with a compromised performance status.

Summary of Evidence

- Of the 46 references cited in the ACR Appropriateness Criteria® Resectable Stomach Cancer
document, all of them are categorized as therapeutic references, including 22 well-designed studies and 3 good-quality studies. There are 21 references that may not be useful as primary evidence.

- The 46 references cited in the ACR Appropriateness Criteria® Resectable Stomach Cancer document were published between 1965 and 2015.
- While there are references that report on studies with design limitations, 25 well-designed or good-quality studies provide good evidence.

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria® through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

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**Variant 1:** A 60-year-old man with uT3N1M0 gastric body adenocarcinoma...

**Variant 2:** An 80-year-old woman with uT3N1M0 gastric body adenocarcinoma...

**Variant 3:** A 57-year-old man with uT4N2M0 gastric body adenocarcinoma....

**Variant 4:** A 54-year-old man with EUS uT2NxM0 gastric cardia adenocarcinoma...
Variant 5: A 63-year-old woman with uT2N1 antral adenocarcinoma status...

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