Combined Modality Therapy of Localized Gastric and Esophageal Cancers

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Abstract
Gastric and esophageal cancers continue to be a significant health problem. The incidence of gastric and esophageal cancers has been increasing, especially in white men. Gastric and esophageal cancers have high rates of locoregional and distant failure, resulting in poor overall survival. Therefore, patients with gastric and esophageal cancer may benefit from combined modality therapy. Adjuvant chemoradiation has been shown to improve survival in gastric and gastroesophageal cancers in a phase III trial. In esophageal cancer, most randomized trials have not shown a survival benefit for preoperative chemotherapy or chemoradiation, although these approaches are widely used. This article reviews the role of staging, surgery, and adjuvant and preoperative therapies in the management of localized gastric and esophageal cancers. (JNCCN 2006;4:375–382)

Staging
Accurate staging plays a critical role in formulating an appropriate treatment plan for patients with gastric and esophageal cancers. Esophagogastroduodenoscopy (EGD) provides visualization of the upper gastrointestinal tract and enables determination of the size, extent, and location of the tumor in the stomach and esophagus. EGD enables biopsy of the tumor for pathologic diagnosis and also helps with evaluation for second primaries and associated conditions such as Barrett’s esophagus, atrophic gastritis, and Helicobacter pylori infection. Computed tomography (CT) scans are used to evaluate the extent of disease and presence of distant metastasis. However, CT scans have limited accuracy for determining the T and N stages. Patients with esophageal tumors at or above the carina should also undergo bronchoscopy to evaluate for tracheal invasion and tracheoesophageal fistula. In patients with gastric cancer, laparoscopy can help evaluate for peritoneal spread.

Endoscopic ultrasonography (EUS) has become an important part of the staging workup because of its superior accuracy for T and N staging compared with other modalities. EUS has been shown to have an accuracy of over 80% for T staging and around 75% for N staging for esophageal and gastric cancers. EUS-guided fine needle aspiration can further improve the accuracy of EUS for nodal staging by providing cytologic verification of regions. For gastric cancer, it is particularly high in regions such as Eastern Europe, East Asia, and South America, whereas the incidence of esophageal cancer is high in the Middle East, East Asia, and Eastern Europe. Although the incidence of gastric cancers has declined over the past few decades, proximal gastric and distal esophageal cancers have increased in recent years, especially in certain populations such as white men.
nodal involvement. EUS should be performed with dedicated radial echoendoscopes (5–20 MHz) that provide a 12-cm diameter range of view. High-frequency ultrasound probes, or miniprobe (12–20 MHz), can provide better image quality and higher accuracy for assessing the depth of invasion, but these probes have a limited range of view and are not suitable for assessing nodal involvement.10,11

Positron emission tomography (PET) also plays an important role in staging. PET has been shown to provide incremental value over CT in ascertaining nodal involvement and distant metastasis in esophageal cancer patients.12 PET has an accuracy of around 90% for detecting distant metastasis from esophageal cancer and has been shown to be superior to CT in this regard.13,14 PET can also predict survival and response to chemoradiation in esophageal cancer patients.14 The data for the role of PET in gastric cancer are more limited, but some studies indicate that PET has higher specificity than CT for nodal staging in gastric cancer.15,16

In addition to a thorough staging evaluation, multidisciplinary evaluation is critical for formulating appropriate treatment recommendations. Ideally, multidisciplinary evaluation should include assessment by surgical oncology, medical oncology, radiation oncology, and gastroenterology.

**Surgery**

Surgery serves as the primary treatment for localized gastric cancer and as one of the definitive therapies for localized esophageal cancer. Patients undergoing surgery at high-volume centers and specialized cancer centers appear to have better outcomes. Multiple studies have shown decreased postoperative mortality after esophagectomy in high-volume hospitals compared with low-volume hospitals.17 Moreover, patients who underwent gastrectomy at National Cancer Institute (NCI)-designated cancer centers were found to have lower surgical mortality compared with patients at other high-volume hospitals.18

Controversies exist about the optimal extent of surgery and the best surgical approach. Retrospective studies indicate that more extensive lymph node dissection may improve outcomes for gastric cancer.19,20 However, randomized trials comparing patients undergoing D1 lymphadenectomy (dissection of perigastric lymph nodes and nodes along the celiac, left gastric, hepatic, and splenic vessels) have not shown a significant difference in survival between D1 and D2 lymphadenectomy. However, patients treated with D2 lymphadenectomy had higher rates of postoperative morbidity and mortality.21,22 The current American Joint Committee on Cancer (AJCC) staging system requires pathologic assessment of a minimum of 15 regional nodes for gastric cancer.23

Surgical approaches for esophageal cancer include transhiatal esophagectomy and transthoracic esophagectomy, such as the Ivor Lewis procedure and the 3-hole procedure.1 A transhiatal approach allows avoidance of thoracotomy with potentially reduced morbidity and mortality, whereas a transthoracic approach allows a more thorough lymph node dissection.1 A randomized trial comparing transhiatal and transthoracic esophagectomy showed that perioperative morbidity was higher with transthoracic esophagectomy, but no significant difference was seen in in-hospital mortality between the 2 arms.24 A trend toward higher 5-year survival (39% vs. 29%) and disease-free survival was seen in the transthoracic esophagectomy arm, but this difference was not significant. Minimally invasive esophagectomy or laparoscopic esophagectomy may be an option for some esophageal cancer patients.25,26 Selected patients with early superficial cancers of the stomach and esophagus may also be treated with endoscopic mucosal resection.27

**Gastric Cancer**

**Adjuvant Chemotherapy and Chemoradiation**

High rates of locoregional and distant failure occur after surgery alone for localized gastric cancer.28,29 Therefore, chemotherapy and radiotherapy may play important roles (in addition to surgery). Several prospective randomized trials have evaluated the role of adjuvant chemotherapy in patients with resected gastric cancer, mostly using anthracycline- or cisplatin-based regimens.4 Meta-analyses have also been performed to investigate the role of adjuvant chemotherapy. Earle and Maroun50 performed a meta-analysis of 13 randomized trials from non-Asian countries and reported an odds ratio for death of 0.80 (95% confidence interval [CI], 0.66–0.97) with adjuvant chemotherapy. Janunger et al.31 performed a
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meta-analysis of 21 randomized trials and reported an odds ratio for death of 0.84 (CI, 0.74–0.96) with chemotherapy. Other meta-analyses have reported similar small benefits for adjuvant chemotherapy.\textsuperscript{12–34} Given the modest benefits reported in these meta-analyses, we do not currently recommend adjuvant chemotherapy.

In contrast to adjuvant chemotherapy, a role for adjuvant chemoradiation is now widely accepted, at least in the United States. The Intergroup 0116 Trial was the pivotal study for the role of adjuvant chemoradiation in patients with resected adenocarcinomas of the stomach or gastroesophageal junction (Table 1).\textsuperscript{35} This phase II trial randomized 556 patients with stage IB through IV (T1N1, T2-T4 any N; M0) gastric or gastroesophageal cancer to undergo either surgery alone or surgery followed by adjuvant chemoradiation. This therapy consisted of 1 cycle of 5-fluorouracil (5-FU) and leucovorin followed by radiation therapy (45 Gy) with concurrent bolus 5-FU and leucovorin, followed by 2 more cycles of 5-FU and leucovorin. The 3-year relapse-free survival rate was 31\% in the surgery-alone arm and 48\% in the chemoradiation arm (\textit{P} < .001), whereas the 3-year overall survival was 41\% in the surgery-alone arm and 50\% in the chemoradiation arm (\textit{P} = .005).\textsuperscript{13} Adjuvant chemoradiation also increased the median survival from 27 months to 36 months. Based on this trial, adjuvant chemoradiation has been accepted as the standard of care in the United States.

Although a D2 dissection was recommended in the Intergroup 0116 Trial, 54\% of patients underwent a D0 dissection (less-than-complete removal of perigastric lymph nodes), 36\% a D1 dissection, and 10\% a D2 dissection.\textsuperscript{36} A subsequent analysis of the study showed that the Maruyama Index, a measure of unresected nodal disease, was an independent predictor of survival for the patients in this trial.\textsuperscript{36} Because over half the patients in this trial underwent limited surgeries, whether adjuvant chemoradiation benefits patients undergoing more extensive surgeries remains unclear. Future trials should incorporate surgical quality control as one of the components of the trial.

The Intergroup study underscored the importance of quality assurance for radiotherapy. As many as 35\% of radiation treatment plans in the trial had major or minor protocol violations.\textsuperscript{31} Although most of the protocol violations were corrected before the start of radiotherapy, the high rate of violations indicates that radiation oncologists must pay particular attention to the design of treatment fields in these patients. Consensus guidelines have been published regarding radiation treatment planning for adjuvant chemoradiation in patients with gastric cancer.\textsuperscript{37}

Ongoing trials are evaluating more aggressive regimens of adjuvant chemoradiation. The Cancer and Leukemia Group B (CALGB) is conducting a phase III trial on patients with resected gastric or gastroesophageal cancer.\textsuperscript{46} In one arm, patients who have undergone surgery receive 1 cycle of 5-FU and leucovorin, followed by radiation therapy with infusional 5-FU, followed by 2 more cycles of 5-FU and leucovorin. In the other arm, patients receive 1 cycle of epirubicin, cisplatin, and 5-FU (ECF), followed by radiation therapy with infusional 5-FU, followed by 2 more cycles of ECF. The Radiation Therapy Oncology Group (RTOG) G-0114 Trial has closed recently. In this randomized, phase II trial, patients with resected gastric or gastroesophageal cancer were treated with 2 cycles of cisplatin, paclitaxel, and infusional 5-FU, followed by radiation therapy with concurrent paclitaxel and

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<th>Table 1 Adjuvant Chemoradiation for Gastric Cancer: Results from the Intergroup 0116 Trial</th>
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<tr>
<td><strong>Toxicity</strong></td>
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<td>Gastrointestinal toxicity ≥ grade 3</td>
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<td><strong>Relapse-free survival</strong></td>
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<td><strong>Overall survival</strong></td>
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<td>Regional relapse*</td>
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<td>Distant relapse*</td>
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*At first relapse.
infusional 5-FU, or treated with 2 cycles of cisplatin and paclitaxel, followed by radiation therapy with concurrent cisplatin and paclitaxel. The 5-FU–containing arm of this trial had to be closed early because toxicities exceeded prespecified boundaries. Final results are pending from this trial.

**Preoperative Chemotherapy and Chemoradiation**

Preoperative or neoadjuvant therapy has certain potential advantages over postoperative or adjuvant therapy. Preoperative therapy may downstage the cancer and increase resectability. Tissue perfusion is uninterrupted in the preoperative setting, leading to better drug delivery and oxygenation, which enhance the effects of radiation. Preoperative therapy may also sterilize the operative field and decrease the risk of tumor seeding.

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Study evaluated the role of preoperative chemotherapy through a phase III trial. In this trial, 503 patients with adenocarcinoma of the stomach, gastroesophageal junction, or lower esophagus were randomized to undergo either surgery alone or surgery with 3 preoperative and 3 postoperative cycles of ECE. Patients treated with chemotherapy had higher progression-free survival with a hazard ratio of 0.66 (CI, 0.53–0.81; P = .0001). Moreover, chemotherapy increased the 5-year overall survival from 23% to 36%, with a hazard ratio of 0.75 (CI, 0.60–0.93; P = .009). However, this trial has only been presented in abstract form, and publication of the full results is awaited.

Small prospective trials have evaluated preoperative chemoradiation for gastric and gastroesophageal junction cancers. In a multi-institutional trial, 33 patients were treated with 2 cycles of 5-FU, leucovorin, and cisplatin, followed by radiation therapy with concurrent infusional 5-FU. Subsequently, 28 patients underwent surgery. The pathologic complete response rate was 30%, the R0 resection rate was 70%, and the 2-year survival was 54%. In another prospective trial, 41 patients were treated with 2 cycles of 5-FU, paclitaxel, and cisplatin, followed by radiotherapy with concurrent paclitaxel and infusional 5-FU. In this study, 40 of 41 patients underwent surgery. The pathologic complete response rate was 20%, the R0 resection rate was 78%, and the median survival was beyond 36 months. The RTOG conducted a phase II trial, RTOG 99-04, in which 49 patients with potentially resectable gastric cancer were treated with 2 cycles of induction chemotherapy with 5-FU, leucovorin, and cisplatin, followed by radiation therapy with concurrent 5-FU and paclitaxel, followed by surgical resection. Among 43 evaluable patients, the pathologic complete response rate was 27% and the R0 resection rate was 77%. Grade 4 toxicity occurred in 21% of patients. The results from these preoperative chemoradiation trials appear promising, and randomized trials are warranted to compare preoperative and postoperative chemoradiation.

**Definitive Chemoradiation**

Surgery serves as the mainstay of treatment for patients with resectable gastric cancer. However, patients with unresectable disease and patients for whom surgery is not possible may be treated with definitive chemoradiation. Small randomized trials performed a few decades ago showed that overall survival was higher in patients treated with radiation therapy and concurrent 5-FU chemotherapy than in patients treated with radiation therapy alone. Retrospective studies have shown that patients treated with definitive chemoradiation have median survival of 12 to 14 months. In addition to definitive chemoradiation, preoperative chemoradiation may play an important role in localized, unresectable, or borderline resectable gastric cancer.

**Esophageal Cancer**

**Preoperative Chemotherapy and Chemoradiation**

Patients with esophageal cancer also have high rates of locoregional and distant failure and may therefore benefit from chemotherapy and radiotherapy. Multiple randomized trials have evaluated the role of preoperative chemotherapy in esophageal cancer. In the Intergroup 0013 Trial, 440 patients with localized, resectable esophageal cancer were randomized to undergo either surgery alone or preoperative chemotherapy with 5-FU and cisplatin followed by surgery. Preoperative chemotherapy did not significantly increase overall survival (P = .53). The median survival was 14.9 months for the surgery-alone arm and 16.1 months for the chemotherapy arm, whereas the 3-year survival was 26% for the surgery-alone arm and 23% months for the chemotherapy arm. Moreover, preoperative chemotherapy did not change the rate of locoregional or distant relapse. The Medical Research Council conducted a randomized trial in which 802
patients with resectable esophageal cancer were randomized to undergo either surgery alone or surgery with preoperative 5-FU and cisplatin. Radiation therapy could be administered in either arm of the trial, based on physician preference. In this trial, overall survival was significantly higher in patients undergoing preoperative chemotherapy ($P = .004$). The median survival was 512 days for the chemotherapy arm and 405 days for the surgery-alone arm, whereas the 2-year survival was 43% for the chemotherapy arm and 34% months for the surgery-alone arm. These 2 trials have shown conflicting results about the role of preoperative chemotherapy. Moreover, meta-analyses of randomized trials have not shown any survival benefit from preoperative chemotherapy compared with surgery alone.49,50

Several randomized trials have investigated the role of preoperative chemoradiation for esophageal cancer (Table 2). Walsh et al.51 randomized 113 patients with esophageal adenocarcinoma to undergo either surgery alone or surgery after preoperative radiation therapy with concurrent 5-FU and cisplatin. Patients undergoing preoperative chemoradiation had significantly higher overall survival ($P = .01$). The median survival was 16 months for the preoperative chemoradiation arm and 11 months for the surgery-alone arm, and the 3-year survival was 32% for the preoperative arm and 6% for the surgery-alone arm. However, other randomized trials have not reported a survival advantage from chemoradiation. Bosset et al.52 randomized 282 patients with esophageal squamous cell carcinoma to undergo either surgery alone or surgery with preoperative radiotherapy and concurrent cisplatin. The median survival was 18.6 months in both arms of this trial ($P = .78$). Disease-free survival was significantly longer in patients undergoing preoperative chemoradiation, but operative mortality was also higher in the chemoradiation arm.

Urba et al.53 randomized 100 patients with esophageal carcinoma to undergo either surgery alone or surgery with preoperative radiotherapy and concurrent 5-FU, cisplatin, and vinblastin. The median survival was 17.6 months in the surgery-alone arm and 16.9 months in the arm with surgery and chemoradiation. The 3-year survival rate was higher for patients in the chemoradiation arm (30%) than those in the surgery-alone arm (16%), but this difference did not reach statistical significance ($P = .15$). Two other recently reported randomized trials have also shown no survival benefit from preoperative chemoradiation compared with surgery alone.54,55 In contrast, the recently reported CALGB 9781 trial showed a significant survival benefit from preoperative chemoradiation.56 In this trial, patients were randomized to undergo either surgery alone or preoperative radiation therapy with concurrent 5-FU and cisplatin followed by surgery. Although the accrual goal of the CALGB trial was 500 patients, the trial was closed after only 56 patients entered because of poor accrual. Patients in the preoperative chemoradiation arm had significantly higher overall survival compared with those in the surgery-alone arm. The median survival was 4.5 years for the preoperative chemoradiation arm and 1.8 years for the surgery-alone arm ($P = .02$), and the 5-year survival was 39% and 16%, respectively. In interpreting the results from the CALGB trial, the low number of patients in the trial, the inability of the trial to meet its accrual goal, and the negative results from multiple other larger trials must be considered. Meta-analyses of randomized trials have shown that

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<th>Study</th>
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<th>Radiotherapy</th>
<th>Median Survival (mo)</th>
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<td>Urba et al.53</td>
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<td>45.6 Gy, 38 twice-daily fractions</td>
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preoperative chemoradiation significantly increases the 3-year survival but not the 1-year survival, compared with surgery alone.\textsuperscript{50,57} However, even in the meta-analyses, the magnitude of benefit from preoperative chemoradiation appears to be small.\textsuperscript{50} Moreover, such meta-analyses should be regarded as hypothesis-generating and not definitive evidence. Therefore, conflicting data exist about a survival benefit from preoperative chemoradiation for esophageal cancers.

**Definitive Chemoradiation**
Chemoradiation can be used as definitive treatment for esophageal cancers. The RTOG 85-01 Trial showed chemoradiation to be superior to radiation therapy alone for definitive treatment of esophageal cancer.\textsuperscript{56,59} In this trial, 123 patients with T1-3, N0-1 esophageal cancer were randomized to undergo either radiation therapy alone (64 Gy), or radiation therapy (50 Gy) with concurrent 5-FU and cisplatin. The median survival was 8.9 months for the radiotherapy arm and 12.5 months for the chemoradiation arm. The 5-year survival was 0% for the radiotherapy arm and 26% for the chemoradiation arm (\textit{P} < .001). A recent meta-analysis of 13 randomized trials showed that concurrent chemoradiation significantly increased survival and reduced local recurrence, compared with radiation therapy alone, although sequential chemotherapy and radiation therapy did not improve outcomes compared with radiation therapy alone.\textsuperscript{60} The Intergroup 0123 Trial compared chemoradiation with standard-dose (50.4 Gy) and high-dose (64.8 Gy) radiation therapy.\textsuperscript{61} The authors noted no significant difference in median survival, 2-year survival, or locoregional failure between the 2 arms. Based on this trial, 50 to 50.4 Gy was accepted as the standard dose for definitive chemoradiation for esophageal cancers.

Two randomized trials compared chemoradiation alone and chemoradiation followed by surgery.\textsuperscript{62,63} In a study performed in Germany, 172 patients with T3-4 N0-1 esophageal squamous cell carcinoma were randomized to undergo either induction chemotherapy followed by chemoradiation (40 Gy) and surgery, or induction chemotherapy followed by chemoradiation alone (\textgeq; 65 Gy).\textsuperscript{64} No significant difference was found in overall survival between the groups. Patients in the chemoradiation-alone arm had a median survival of 14.9 months and those in the surgery arm had a median survival of 16.4 months. Local progression-free survival was higher in the surgery arm, but treatment-related mortality was also higher. In a French study, patients with esophageal cancer who showed at least a partial response to chemoradiation (46 Gy) were randomized to undergo surgery or further chemoradiation (additional 15-20 Gy).\textsuperscript{65} These authors also noted no difference in overall survival between the 2 arms. Some limitations of these studies should be noted, such as high postoperative mortality and low power. Furthermore, the survival curves in the German trial appeared to diverge after 3 years in favor of the surgery arm.

**Conclusions**
Combined modality therapy plays an important role in the management of localized gastric and esophageal cancers because patients with these diseases have high rates of locoregional and distant failure. Appropriate staging and multidisciplinary management are critical. Surgery is the primary therapy for gastric cancer. Based on the results of the Intergroup 0116 Trial, adjuvant chemoradiation is indicated after surgical resection for most patients with gastric and gastroesophageal cancer (except patients with stage T1 N0 disease and selected patients with stage T2 N0 disease). Preoperative treatments are also under investigation for gastric cancer. For patients with esophageal cancer, treatment options include surgery, preoperative chemoradiation followed by surgery, and definitive chemoradiation. Randomized trials have shown conflicting results about a survival benefit from preoperative chemoradiation for patients with esophageal cancer. Randomized trials in esophageal cancer have also failed to show a survival benefit for surgery and chemoradiation compared with chemoradiation alone. Our inability to individualize therapy for localized upper gastrointestinal cancer patients remains a major setback. Further improvements in the outcome are essential and may be realized through investigations of the molecular profile of cancer and patient genetics.

**References**

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