Adjuvant (Postoperative) Therapy for Esophageal Cancer

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KEYWORDS

• Esophageal cancer • Gastroesophageal junction cancer • Adjuvant • Chemoradiation
• Chemotherapy

KEY POINTS

- In the past 10 to 15 years, completed clinical trials have demonstrated that some therapy in addition to surgery improves survival in patients with locally advanced cancers of the esophagus and gastroesophageal (GE) junction.
- In Europe and the United States, a common approach is to administer perioperative chemotherapy for resectable GE junction adenocarcinoma, based on the MAGIC study.
- Several trials, including the recent CROSS trial, also show a benefit for preoperative chemoradiation for tumors of the esophagus and GE junction.
- In Asia, recent trials in gastric adenocarcinoma have demonstrated a survival benefit for adjuvant chemotherapy, either with 1 year of the oral 5-fluorouracil prodrug S-1 or with 6 months of capecitabine/oxaliplatin therapy.
- A clearly proven strategy for squamous cell carcinomas is chemoradiation, administered either as preoperative therapy or as definitive treatment for patients who subsequently achieve a clinical complete response.

INTRODUCTION

In the United States, cancers of the esophagus and gastroesophageal (GE) junction are uncommon but aggressive. In 2013 an estimated 17,990 patients will be diagnosed, with an estimated 15,210 deaths from this disease.[1] These poor outcomes notwithstanding, survival has actually improved over time. In the period between 1975 to 1977 and 2000 to 2007, 5-year survival for esophageal cancers has increased from 5% to 19%.

Adenocarcinomas and squamous cell carcinomas (SCCs) account for 98% of all cases of esophageal cancer. SCCs normally occur in the upper two-thirds of the esophagus while adenocarcinomas occur in the lower third and at the GE junction. While cases of proximal esophageal SCCs have steadily declined (because of a parallel decrease in alcohol and tobacco consumption), the incidence of adenocarcinoma of the distal esophagus and GE junction has increased 4% to 10% per year among men in the United States since 1976.[2,3] Adenocarcinomas now account for more than 75% of esophageal tumors, and their increase is thought to be due to an increased incidence of gastroesophageal reflux disease[4] and obesity.[5]

In comparison to its relative rarity in the United States, esophageal cancer (predominantly SCC) is endemic in parts of East Asia, which account for more than half of the approximately 500,000 cases that develop per year (this number does not fully take into account GE junction tumors,

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which may variously be categorized as gastric cancers).[6]

This review focuses specifically on adjuvant (postoperative) therapies for locally advanced esophageal and GE junction adenocarcinomas and SCCs (T3–4 or node-positive tumors), namely postoperative chemoradiation or chemotherapy. Where relevant, strategies that incorporate or consist of preoperative treatments are also discussed.

ADJUVANT CHEMORADIATION

In the United States, a standard of care is postoperative chemoradiation for resected GE junction adenocarcinomas, based primarily on the results of the Intergroup 116 trial.[7] This trial randomized 556 patients with gastric adenocarcinomas (20% of whom had tumors that involved the GE junction) to adjuvant chemotherapy and chemoradiation with bolus 5-fluorouracil (5-FU)/leucovorin versus observation alone following surgery. Patients who received adjuvant chemoradiation had an improvement in relapse-free survival (RFS) (3-year RFS 48% vs 31%, $P<.001$) and overall survival (OS) (3-year OS 51% vs 40%, $P = .005$). Despite these positive results, this trial is frequently criticized because of the relatively inadequate surgical resections that were performed: 54% of patients had less than a D1 or D2 resection, which is less than a complete dissection of the involved lymph nodes. It has been argued that radiation in this setting compensated for inadequate surgery because the greatest impact of adjuvant chemoradiation was a reduction in local recurrence of cancer. Such benefits may not be seen for radiotherapy if a more complete D1 or D2 surgical resection is undertaken. The size of the radiotherapy field for GE junction cancers, extending from the surgical bed high into the mediastinum to cover the anastomosis, is likely to exacerbate toxicity, and reinforces the application of preoperative rather than postoperative chemoradiation for these patients.

Based on the results of the Intergroup trial, the CALGB (Cancer and Leukemia Group B) 80101 trial attempted to intensify adjuvant chemoradiation by adding the ECF regimen (epirubicin/cisplatin/infusional 5-FU) as part of adjuvant treatment combined with 5-FU and radiation. Five hundred forty-six patients with gastric cancer (30% of whom had tumors involving the GE junction and proximal stomach) were enrolled. The standard arm consisted of systemic bolus 5-FU/leucovorin preceding and following chemoradiation with infusional 5-FU while the experimental arm intensified the systemic chemotherapy by replacing the bolus 5-FU/leucovorin with the ECF regimen. Results were recently presented in abstract form, and reveal no improvement in 3-year disease-free survival (DFS; 47% vs 46%) or OS (52% vs 50%) with the addition of an anthracycline and platinum compound to 5-FU.[8] These results are also virtually identical to the outcomes in the adjuvant chemoradiation arm of the Intergroup 116 trial. These findings indicate that 5-FU monotherapy, combined with radiation, remains a standard of care, and that adding cisplatin and epirubicin to adjuvant chemotherapy failed to improve survival. ECF should not be used as an adjuvant chemotherapy regimen, although preoperative and postoperative ECF without radiation therapy remains a care standard (see later discussion).

The results of the aforementioned studies are summarized in **Table 1**.

ADJUVANT CHEMOTHERAPY

In comparison with chemoradiation, trials in East Asia of resectable gastric cancer have frequently focused on postoperative chemotherapy alone. To date, 2 large phase III trials have demonstrated a benefit for this approach. These data support the use of adjuvant fluoropyrimidines as monotherapy, and combination chemotherapy with a fluoropyrimidine plus a platinum agent. The results are summarized in **Table 2**, but should be interpreted with considerable caution because these trials have exclusively enrolled patients with gastric adenocarcinoma. In East Asia, less than 10% of tumors occur in the proximal stomach/GE junction, making it unclear whether they are applicable to the patient population discussed in this article.

The ACTS-GC (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer) study was performed in Japan. In this study of 1059 patients with completely resected (R0) stage II/III gastric cancer who had undergone D2 resections, patients were randomized to 1 year of adjuvant S-1 versus observation.[9] S-1 is a mixture of tegafur (an oral 5-FU prodrug), gimeracil (a dihydropyrimidine dehydrogenase inhibitor that may potentiate the effect of 5-FU), and oteracil (which may reduce the gastrointestinal toxicity of 5-FU). Five-year outcomes for this trial were recently updated, confirming that adjuvant S-1 is associated with significant improvements in 5-year RFS (65.4% vs 53.1%, hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.54–0.79) and OS (71.7% vs 61.1%, HR 0.67, 95% CI 0.54–0.83) compared with observation alone.[10] Subgroup analyses revealed benefit for all groups, including by stage and histologic type.

The second trial is the CLASSIC trial (capecitabine and oxaliplatin adjuvant study in stomach