Controversies and Consensus in Preoperative Therapy of Esophageal and Gastroesophageal Junction Cancers

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KEYWORDS

• Adenocarcinoma • Squamous cell carcinoma • Preoperative • Adjuvant
• Chemoradiation • Chemotherapy

KEY POINTS

- Chemoradiation is the standard of care for unresectable esophageal cancer and an option for squamous cell carcinoma (SCC); surgery reserved is for persistent/recurrent disease.
- There are limited and conflicting data supporting a role for preoperative or postoperative chemotherapy for resected SCC.
- Preoperative chemoradiation and surgery is a standard of care for esophageal/gastro-esophageal junction (GEJ) adenocarcinoma.
- Other options for GEJ adenocarcinomas include perioperative chemotherapy or adjuvant chemoradiation.
- Adjuvant chemotherapy alone is an option for gastric adenocarcinoma based on Asian studies, where fewer than 10% of tumors involve the proximal stomach or GEJ.

INTRODUCTION

Esophageal cancer, an uncommon but highly virulent malignancy in the United States, will be diagnosed in 16,910 patients in 2016, with 15,690 deaths.[1] It is the seventh leading cause of death in men in the United States. In comparison with its relative rarity in the United States, esophageal cancer (predominantly squamous cell carcinoma [SCC]) is endemic in parts of East Asia, which accounts for more than one-half of the approximately 500,000 cases that develop per year (this number does not fully

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take into account gastroesophageal or gastroesophageal junction (GEJ) tumors, which may variously be categorized as gastric cancers).[2]

SCC and adenocarcinoma account for 98% of all cases of esophageal cancer. SCCs typically occur in the proximal two-thirds of the esophagus, whereas adenocarcinomas are found in the distal one-third and at the GEJ. Although cases of SCC have declined steadily, the incidence of adenocarcinoma of the distal esophagus, GEJ and gastric cardia has increased 4% to 10% per year among US men since 1976, so that it now comprises 75% of all tumors.[3,4]

For locally advanced esophageal cancer, surgery remains the mainstay of treatment. Numerous studies—that have included both adenocarcinoma and SCC histologies and focused on tumors from the esophagus/GEJ and/or stomach—have evaluated preoperative and postoperative strategies for locally advanced disease, including chemotherapy or chemoradiation. As a whole, these studies show that some treatment in addition to surgery clearly improves outcomes. This review article discusses these studies; where relevant, we note whether these studies primarily enrolled patients with esophageal/GEJ or gastric tumors.

PREOPERATIVE CHEMOTHERAPY

A strategy of perioperative chemotherapy is the predominant approach in Europe, based primarily on the phase III MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial performed in the UK.[5] This trial randomized 503 patients with gastric cancer (26% of whom had tumors in the lower esophagus/GEJ) to 3 cycles (9 weeks) each of preoperative and postoperative ECF (epirubicin/cisplatin/5-fluorouracil [5-FU]) and surgery or surgery alone. Perioperative chemotherapy resulted in significant improvement in 5-year overall survival (OS; 36% vs 23%; $P = .009$), establishing this regimen as a standard of care.

A similar degree of benefit was also noted in the contemporaneous French FFCD 9703 trial of 224 patients with esophagogastric adenocarcinoma.[6] Patients were randomized to 6 cycles (18 weeks) of perioperative 5-FU/cisplatin followed by surgery versus surgery alone. Perioperative chemotherapy on this trial was associated with a significant improvement in 5-year disease-free survival (DFS; 34% vs 19%; $P = .003$) and OS (38% vs 24%; $P = .02$). Although comparisons between different clinical trials must be made cautiously, the survival benefit seen with 5-FU/cisplatin on this trial seems to be nearly identical to that seen with ECF in the MAGIC trial.

The benefit of the anthracycline—and the duration of preoperative therapy—has now been disputed definitively by the MRC OEO-5 study which has so far only been presented in abstract form.[7] This study randomized 897 patients with esophageal/GEJ adenocarcinomas to preoperative chemotherapy with either 6 weeks of 5-FU/cisplatin or 12 weeks of ECX (epirubicin/cisplatin/capecitabine) chemotherapy. Although the pathologic response rate was improved in the ECX group versus the 5-FU/cisplatin group (including a pathologic complete response [pCR] rate of 11% vs 3% in the patients who underwent surgery), there was no difference in median progression-free survival between the groups (PFS; 1.78 vs 1.53 years; $P = .058$) or OS (2.15 vs 2.02 years; $P = .86$).

The OEO-5 study has therefore also raised the provocative suggestion that as little as 6 weeks of preoperative chemotherapy conveys the same OS benefit as 12 weeks of chemotherapy. Although this may be counterintuitive based on the MAGIC and FFCD studies, as well as other studies in gastric cancer that have administered 6 to 12 months of adjuvant chemotherapy,[8,9] these results are not