Review Article on Current Management of Upper Gastrointestinal Malignancies

Neoadjuvant and adjuvant therapy in esophageal cancer

Jennifer A. Weiss, Shikha Jain

Division of Hematology and Oncology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

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Correspondence to: Jennifer A. Weiss, MD. University of Illinois at Chicago, 840 S. Wood St., Ste 820-E CSB MC 713, Chicago, IL 60612, USA. Email: weiss12@uic.edu.

Abstract: Esophageal cancer is an aggressive malignancy that carries a high mortality rate. The treatment of locally advanced resectable esophageal cancer requires a multimodal approach involving chemotherapy, radiation therapy, and surgical resection. Optimal treatment combinations and sequences for squamous cell carcinoma (SCC) versus adenocarcinoma (AC) histological subtypes are still being determined. For very early stage esophageal cancers, endoscopic therapies or surgical resection without chemotherapy and radiation are preferred. Neoadjuvant chemoradiation followed by surgical resection has been the standard in locally advanced resectable esophageal cancer based on the landmark CROSS trial. Definitive chemoradiation is recommended for patients who are not surgical candidates or decline surgery. Perioperative chemotherapy without radiation can be considered for lower esophageal AC and gastroesophageal (GE)-junction AC based on landmark MAGIC and FLOT4 trials. Additional trials are underway to compare preoperative chemoradiation to perioperative chemotherapy in esophageal and GE-junction ACs. Thus far, targeted therapies against vascular endothelial growth factor (VEGF) and human epidermal growth factor receptor 2 (HER2) have not been successful in the neoadjuvant/adjuvant setting. The roll of immunotherapy in perioperative/adjuvant setting is promising. Based on the CheckMate 577 trial, adjuvant nivolumab should be considered for all patients following neoadjuvant chemoradiation and R0 resection with residual pathologic disease. Additional trials involving various immunotherapy agents are underway.

Keywords: Esophageal cancer; neoadjuvant; perioperative; immunotherapy

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Esophageal cancer is an aggressive gastrointestinal malignancy that generally has a poor prognosis. The most common histological subtypes are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Esophageal SCC has been linked to tobacco, alcohol, hot beverages, and nitrosamines, whereas Barrett's esophagus, gastroesophageal (GE) reflux disease, obesity, and tobacco consumption are more common risk factors for esophageal AC (1). In the United States, rates of esophageal SCC have been decreasing while the rates of esophageal AC have been rising. There is a 2-fold to 3-fold higher incidence of esophageal cancer in men than women (2).

The treatment of non-metastatic esophageal cancer benefits from a multidisciplinary approach including surgery, radiation oncology, and medical oncology. Carcinoma *in situ* and some very early-stage esophageal cancers may be amenable to endoscopic resection and ablation (3). Esophagectomy alone can be utilized for early-stage esophageal cancers without high-risk features in patients who are surgical candidates. Neoadjuvant chemoradiation followed by surgery has become the mainstay treatment stage II and III resectable esophageal cancer for both SCC and AC based on the landmark CROSS trial (*Table 1*).

The CROSS trial was a phase III randomized trial that included 366 patients with resectable esophageal or GE-

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junction tumors (T1N1M0 or T2-3N0-1M0) in 2004 to 2008. Patients were randomized to receive chemoradiation with carboplatin and paclitaxel with concurrent radiotherapy followed by surgery compared to surgery alone (4); 75% of the patients had AC and 23% had SCC. The study found a significant improvement in overall survival (OS) with median OS of 49.4 months in the chemoradiotherapy-surgery arm compared to 24.0 months in the surgery alone arm [hazard ratio (HR), 0.657; 95% confidence interval (CI), 0.495 to 0.871; P=0.003]. An OS benefit was seen both SCC and AC subtypes. Complete resection with no tumor within 1 mm of the resection margins (R0) was achieved in 92% of patients in the chemoradiotherapy-surgery group versus 69% in the surgery group (P<0.001). A pathological complete response was observed in 28 of 121 patients with AC (23%) versus 18 of 37 with SCC (49%) (P=0.008) who underwent chemoradiotherapy (4). A long-term follow-up of the CROSS trial found continued OS benefit at 84.1 months (range, 61.1–116.8 months), median OS was 48.6 months in chemoradiotherapy-surgery arm and 24.0 months in the surgery alone arm (HR, 0.68; 95% CI, 0.53–0.88; P=0.003) (12). Median OS for patients with SCC was 81.6 months in the chemoradiotherapy-surgery arm and 21.1 months in the surgery alone arm (HR, 0.48; 95% CI, 0.28–0.83; P=0.008); for patients with ACs, OS was 43.2 months in the chemoradiotherapy-surgery arm and 27.1 months in the surgery alone arm (HR, 0.73; 95% CI, 0.55–0.98; P=0.038) (12).

Based on the CROSS trial, chemoradiation therapy followed by surgery has become the standard approach for patients with locally advanced resectable esophageal cancer. Some studies suggest for esophageal SCC chemoradiation therapy followed by surgery compared to definitive chemoradiation without surgery offers benefit in local control but does not improve survival, while others have shown survival benefit to adding surgical resection to chemoradiation (13-16). At this time, chemoradiation therapy followed by surgery is generally preferred for resectable esophageal SCC in patients who are medically fit. Definitive chemoradiation is recommended for cervical esophageal cancer, unresectable disease (cT4b), or patients that decline or are unfit for surgery (17,18).

Neoadjuvant chemoradiation typically involves platinum-based combination chemotherapy, such as carboplatin and paclitaxel used in the CROSS trial (4). Other chemotherapy regimens frequently used for chemoradiation include leucovorin, fluorouracil, and oxaliplatin (FOLFOX) or fluorouracil and cisplatin (19). The PROTECT trial is an ongoing clinical trial (NCT02359968) comparing preoperative chemoradiation with paclitaxel-carboplatin versus FOLFOX for resectable esophageal and GE-junction cancers (20). Neoadjuvant chemoradiation with fluorouracil and cisplatin has shown OS benefit compared to surgery alone for resectable esophageal cancer in the CALGB 9781 trial (5). In the CALGB 80803 trial, patients with esophageal and GE-junction AC received a baseline positron emission tomography (PET) imaging, followed by induction chemotherapy with FOLFOX or carboplatin plus paclitaxel followed by repeat PET imaging prior to chemoradiation and surgical resection; those who were considered PET non-responders (<35% decrease in standardized uptake value) were crossed over into the alternative chemotherapy arm during radiation (6). While early response PET imaging has not become standard practice, the study was notable for longer OS in patients with early PET response, especially in the FOLOX arm who has an impressive 53% 5-year OS (6). The patient's performance status and comorbidities should be considered in choosing a chemoradiation regimen.

At this time, neoadjuvant chemoradiation followed by surgery is preferred in advanced resectable esophageal cancer as discussed above. However, perioperative chemotherapy followed by surgery can be considered for esophageal AC especially in the lower esophagus based on the MAGIC and FLOT4 trials. The MAGIC trial randomized patients with operable gastric, GE-junction, and lower esophageal ACs to preoperative and postoperative epirubicin, cisplatin, and infused fluorouracil (ECF) (n=250) compared to surgery alone (n=253) from 1994–2002 (7). The 5-year survival rates were 36.3% (95% CI, 29.5–43.0%) for the chemotherapy group compared to 23.0% (95% CI, 16.6–29.4%) for the surgery alone group. About 26% of patients on the trial had GE-junction or lower esophageal ACs. In the FLOT4 trial, neoadjuvant plus adjuvant chemotherapy with FLOT (fluorouracil plus leucovorin, oxaliplatin and docetaxel) was compared to ECF or ECX (epirubicin, cisplatin, and capecitabine) in locally advanced resectable GE-junction AC (8). Esophageal cancers outside of the GE-junction where not included in the FLOT4 trial. There was a significant improvement in OS, with median OS in the FLOT arm of 50 months (38.33–not reached) versus 35 months (27.35–46.26 months) in the ECF/ECX arm. FLOT and ECF/ECX had similar rates of serious adverse events in both groups. Based on this data, the FLOT regimen is preferred over ECF for

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Table 1 Summary of reviewed esophageal cancer trials

Trial name	Year	Cancer subtype	Intervention
CROSS (4)	2012	AC and SCC	Chemoradiation with CP followed by surgery *vs.* surgery alone
CALGB 9781 (5)	2008	AC and SCC	Neoadjuvant chemoradiation with CF *vs.* surgery alone
CALGB 80803 (6)	2021	AC	PET responsiveness after induction chemotherapy with FOLFOX or CP
MAGIC (7)	2006	AC	Perioperative ECF *vs.* surgery alone
FLOT4 (8)	2019	AC	Perioperative FLOT *vs.* ECF or ECX
OE05 (9)	2016	AC	Neoadjuvant ECX *vs.* CF chemotherapy followed by surgery
Neo-AEGIS (preliminary results) (10)	2021	AC	CROSS regimen neoadjuvant chemoradiation to multiple perioperative chemotherapy regimens including the MAGIC and FLOT4 trial regimens
CheckMate 577 (11)	2021	AC and SCC	Adjuvant immunotherapy with nivolumab in patients with stage II and III esophageal and GE-junction cancer following neoadjuvant chemoradiation and an R0 resection who had residual pathologic disease

AC, adenocarcinoma; SCC squamous cell carcinoma; CP, carboplatin and paclitaxel; CF, cisplatin and fluorouracil; PET, positron emission tomography; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; ECF, epirubicin, cisplatin, and fluorouracil; FLOT, fluorouracil plus leucovorin, oxaliplatin and docetaxel; ECX, epirubicin, cisplatin, and capecitabine; GE, gastroesophageal.

perioperative chemotherapy in GE ACs. Perioperative or preoperative cisplatin and fluorouracil (CF) can also be considered for resectable esophageal AC based on the FNCLCC ACCORD-07 trial and the OE05 trial (9,21). In the OE05 trial, no survival benefit was found between neoadjuvant ECX chemotherapy compared to CF alone followed by surgery in patients with resectable esophageal AC. The ECX group was associated with higher toxicity with neutropenia being the most common adverse event; grade 3–4 neutropenia was reported in 23% of the ECX group versus 17% of the CF group (9).

Additional trials are underway to help determine the role of pre/perioperative chemotherapy compared to standard neoadjuvant chemoradiation in resectable esophageal AC. The ESOPEC trial (NCT02509286) is a phase III randomized trial comparing the CROSS trial regimen of chemoradiation with carboplatin and paclitaxel to perioperative FLOT chemotherapy as used in the FLOT4 trial in patients with operable esophageal AC (22). The Neo-AEGIS trial (NCT01726452) is a randomized controlled phase III clinical trial comparing CROSS regimen neoadjuvant chemoradiation to multiple perioperative chemotherapy regimens including the MAGIC and FLOT4 trial regimens in patients with esophageal and GE-junction AC (10). Preliminary results from the Neo-AEGIS trial reports 3-year estimated survival probability in the CROSS arm of 56% (95% CI, 47–64%) and in the MAGIC/FLOT arm of 57% (95% CI, 48–65%), suggesting neoadjuvant chemotherapy without radiation to be non-inferior in this setting (10). However, there was a higher rate of pathologic complete response, pathologic node negativity, and R0 resections in the CROSS neoadjuvant chemoradiation arm. More studies are needed to better elucidate the benefit of combination chemoradiotherapy as compared to chemotherapy alone in the neoadjuvant setting. Both neoadjuvant therapies do improve OS when compared to surgery alone, but the decision on which neoadjuvant modality to utilize should be determined on a case-by-case basis. In patients at higher risk of morbidity, higher risk of cardiac or pulmonary complications or surgical morbidity, it may be of benefit to forego radiation as there is no definitive OS benefit. In patients with larger tumors where there may be a benefit on more rapidly shrinking the tumor for symptom management, combination chemoradiation may be of more utility.

The role of immunotherapy in operable esophageal cancer is being investigated in many trials and recently adjuvant nivolumab has been approved in patients with R0 resection and residual disease based on the CheckMate 577 trial (23). CheckMate 577 was a randomized, double-blind, placebo-controlled phase 3 trial evaluating adjuvant immunotherapy with nivolumab in patients with stage II and III esophageal and GE-junction cancer following neoadjuvant chemoradiation and an R0 resection who had residual pathologic disease (11). Patients were randomly assigned in a 2:1 ratio to receive nivolumab, a fully human

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monoclonal anti-programmed death 1 (PD-1) antibody (n=532) or placebo (n=262) for a maximum of 1 year. The median disease-free survival in the nivolumab group was 22.4 months (95% CI, 16.6–34.0 months), as compared with 11.0 months (95% CI, 8.3–14.3 months) in the placebo group (HR for disease recurrence or death, 0.69; 96.4% CI, 0.56–0.86; P<0.001) (11). Improved disease-free survival was seen in both SCC and AC subtypes. There were similar hazard ratios for disease recurrence or death with tumor-cell PD-L1 expression below 1% compared to 1% or higher. Grade 3–4 adverse events occurred in 13% in the nivolumab group and 6% in the placebo group.

Additional trials are underway evaluating immunotherapy in esophageal cancer including the EA2174 trial (NCT03604991) evaluating perioperative nivolumab with ipilimumab, a monoclonal antibody targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), in resectable esophageal and GE-junction AC. There is an ongoing trial in Asia (NCT04280822) evaluating the role of neoadjuvant immunotherapy with anti-PD-1 monoclonal antibody toripalimab (JS001) in combination with chemotherapy compared to neoadjuvant chemotherapy alone for resectable esophageal SCC. There is also KEYNOTE-585 (NCT03221426) that is evaluating the role of perioperative chemotherapy with or without pembrolizumab, an anti-PD-1 monoclonal antibody, in resectable GE-junction and gastric AC, and KEYNOTE-975 (NCT04210115) evaluating the addition of pembrolizumab to definitive chemoradiation in patients with esophageal cancer who are not candidates for resection. The MATTERHORN trial (NCT04592913) is investigating the addition of neoadjuvant/adjuvant durvalumab, an anti-PD-L1 monoclonal antibody, to FLOT chemotherapy for resectable gastric and GE-junction cancers.

Other targeted therapies have not yet been approved for esophageal cancer in the adjuvant/neoadjuvant setting. Multiple trials have investigated the role of adding anti-vascular endothelial growth factor (VEGF) therapy to the perioperative treatment of esophageal cancer, but so far none have shown significant benefit (24-26). In the metastatic setting, anti-human epidermal growth factor receptor 2 (HER2) therapies have been approved for HER2-overexpressing GE ACs. Recent RTOG 1010 trial investigating the addition of anti-HER2 therapy with trastuzumab to neoadjuvant chemoradiation followed by surgery failed to show benefit in disease-free survival, OS, or pathological complete response compared to neoadjuvant chemoradiation followed by surgery in patients with HER2-overexpressing esophageal AC (27).

In summary, treatment of locally advanced operable esophageal cancer requires a multidisciplinary approach involving medical oncologists, surgeons, and radiation oncologists. Neoadjuvant chemoradiation has been the standard in stage II and III esophageal cancer based on the CROSS trial, however perioperative chemotherapy for lower esophageal AC is likely non-inferior. Further follow-up from these trials is still needed. The addition of immunotherapy is a welcome advancement to the treatment of esophageal cancer and adjuvant nivolumab should be considered for all patients following neoadjuvant chemoradiation and R0 resection with residual pathologic disease based on the CheckMate 577 trial. Additional trials involving various immunotherapy agents are underway.

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Footnote

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