Emerging Multimodality Approaches to Treat Localized Esophageal Cancer

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ABSTRACT

Esophageal cancer has a poor prognosis, with 5-year survival rates ranging from 20% to 35% in the nonmetastatic setting. Despite advances in surgical techniques and optimization of chemoradiotherapy regimens, overall survival benefits have been incremental at best. Esophageal cancer requires a concerted multidisciplinary approach, perhaps more so than any other tumor type given the integral role played by the esophagus in maintaining calorific intake and the propensity for early spread through the lymphatics. This review describes the latest in surgical techniques to minimize postoperative complications and examines previous and ongoing systemic therapy approaches. Strategies that harness a patient's own immune system hold great promise, and shifting checkpoint inhibitors from the metastatic setting to the neoadjuvant/adjuvant setting is currently being evaluated in phase II and III clinical trials. In addition, a much better understanding of the interplay between tumors and their immune microenvironment is clearly needed to better judge how best to engage each patient's immune system, and there will be likely demonstrable differences between early-stage tumors and metastatic disease. This review highlights emerging data, which demonstrate that, in addition to The Cancer Genome Atlas classification of esophageal squamous cell carcinoma having a distinct molecular makeup compared with esophageal adenocarcinoma, there are also differing responses to PD-1 inhibitors. Histology and the underlying immune milieu may have important ramifications for the management of localized disease in the future, above and beyond PD-L1 expression, microsatellite instability status, and tumor mutational burden.

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Background

Esophageal cancer is regarded as an orphan disease in the United States; however, it represents a significant global problem and is the sixth most common cause of cancer-related death worldwide, accounting for approximately 600,000 new cases and just over 500,000 deaths in 2018.[1] Approximately 17,000 new cases are diagnosed each year in the United States,[2] with men having a 2.4-fold higher incidence rate than women. The 5-year survival rates for patients who develop esophageal cancer remain poor, with 5-year overall survival (OS) rates ranging from 12% to 20%[3]; however, improved outcomes are seen in patients with earlier stage disease. Poor outcomes arise from the fact that patients often present with advanced disease and esophageal cancers are inherently resistant to systemic therapy as a result of histologic, molecular, and etiological heterogeneity.

Trimodality approaches involving neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy or perioperative chemotherapy before and after surgery are widely used based on physician preference and access to radiation rather than compelling evidence favoring one approach over another. CRT followed by surgery is predominantly the preferred treatment in the United States, with perioperative chemotherapy more common in Europe. Tumor location plays a key role in deciding the multimodality approach. Definitive CRT is a recognized treatment approach in certain instances of esophageal squamous cell carcinoma (ESCC) and more rarely in esophageal adenocarcinoma (EAC), but currently surgical intervention remains the best chance for cure in EAC. The Siewert classification of the gastroesophageal junction (GEJ) is used to determine whether an esophageal or a gastric treatment paradigm should be pursued. Siewert I and II tumors are often treated with neoadjuvant CRT followed by esophagectomy, whereas most centers treat Siewert III tumors predominantly as a gastric cancer, but given that 2 treatment options exist (bimodality vs trimodality), the most appropriate treatment paradigm for each patient should be decided after multidisciplinary tumor board discussion. The 8th edition of the AJCC Cancer Staging Manual now classifies a tumor involving the GEJ with its epicenter ≤2 cm below the GEJ as

esophageal cancer, with all other tumors below the GEJ now regarded as gastric cancer.[4] Additionally, the recent publication by The Cancer Genome Atlas Research Network confirmed that ESCC and EAC should be treated as separate entities.[5] Next-generation sequencing has identified frequent genomic alterations of *CCND1* and *SOX2* and/or *TP53* genes in ESCC; biologically they are more like squamous cell head and neck cancer, whereas EAC strongly resembles the chromosomally unstable variant of gastric cancer. This review discusses some of the emerging multimodality treatment approaches for esophageal and GEJ carcinomas. Although there is currently a paucity of published data, this article highlights key trials investigating checkpoint inhibitors in operable disease and discusses advances in surgery and chemotherapy regimens that are improving patient outcomes for this challenging disease.

Surgical Advances

OS rates after esophagectomy have been improving in recent years due to the centralization of low-volume, high-risk surgeries in centers of excellence and the increased use of multidisciplinary teams to decide optimal treatment strategies upfront.[6,7] The most common surgical procedures are transthoracic esophagectomies, such as the Ivor Lewis and McKeown techniques and the transhiatal approach. The randomized TIME trial showed that total minimally invasive esophagectomies were associated with less respiratory complications compared with open esophagectomy.[8] Recent data published by Mariette et al[9] suggest that a hybrid minimally invasive esophagectomy, which consists of a laparoscopic abdominal phase (gastric mobilization) and an open right thoracotomy, may have lower incidences of intraoperative and postoperative pulmonary complications (18% vs 30%) and tumor spillage compared with open esophagectomy. An improvement in 3-year OS and disease-free survival (DFS) was seen with the hybrid compared with the open approach (3-year OS: 67% [95% CI, 57%–75%] vs 55% [95% CI, 45%–64%], respectively; DFS: 57% [95% CI, 47%–66%] vs 48% [95% CI, 38%–57%], respectively). The investigators hypothesized that the hybrid approach was associated with reduced surgical trauma and therefore less postoperative pain, leading to less basal lung atelectasis and hence a reduction in pulmonary complications. Clearly, challenges to widespread adoption of any new surgical procedure are surgical training and easy reproducibility of described advances. Irrespective of surgical technique, surgery alone is now only considered for patients with stage I disease and preoperative regimens are standard of care, with achievement of an R0 resection regarded as pivotal for long-term OS.[10,11]

Chemotherapy Approaches

The seminal clinical trials listed in Table 1 evaluated different multidisciplinary treatment strategies for the management of localized esophageal cancer within the past 20 years.[7,12–22] This list is not exhaustive, but it does highlight some of the most salient practice-changing studies. We have also tried to limit the list to trials that focused specifically on esophageal and GEJ cancers, but there is a degree of overlap with some studies including GEJ and proximal gastric cancer. UK MRC OE05,[21] which was an important trial that demonstrated that more chemotherapy is not always in a patient's best interest, compared 2 cycles of preoperative cisplatin/5-FU versus 4 cycles of epirubicin, cisplatin, and capecitabine and found no survival benefit for intensified therapy (median OS, 23.4 vs 26.1 months; hazard ratio [HR], 0.90; 95% CI, 0.77–1.05; P=.19).

At the time of writing, 2 standard regimens are used predominantly in the United States and listed as preferred NCCN regimens: the CROSS regimen of neoadjuvant CRT before esophagectomy or perioperative chemotherapy with either FOLFOX (5-fluorouracil/leucovorin/and oxaliplatin) or FLOT (5-FU/leucovorin/oxaliplatin/docetaxel; for esophageal carcinoma only). Neoadjuvant CRT is the preferred approach for localized resectable disease in the NCCN Guidelines.[23] CROSS evaluated 366 patients with operable stage II/III esophageal cancer.[7] This practice-changing trial showed a higher R0 resection rate (92% vs 69%; P<.001) and a longer median OS (49.4 vs 24.0 months; HR, 0.657; 95% CI, 0.495–0.871; P=.003) in the neoadjuvant CRT/surgery ("trimodality") group compared with the surgery alone ("surgery") group. After a minimum follow-up of 7 years,[24] median OS for patients with ESCC was 81.6 months (95% CI, 47.2–116.0) in the trimodality group and 21.1 months (95% CI, 15.4–26.7) in the surgery group (HR, 0.48; 95% CI, 0.28–0.83; log-rank P=.008), and for patients with EAC, it was 43.2 months (95% CI, 24.9–61.4) in the trimodality group and 27.1 months (95% CI, 13.0–41.2) in the surgery group (HR, 0.73; 95% CI, 0.55–0.98; log-rank P=.038).

Ongoing phase III trials attempting to answer the question of whether to use bimodality or trimodality therapy include ESOPEC (ClinicalTrials.gov identifier: NCT02509286). This study is directly comparing the CROSS regimen with FLOT4 in 438 patients, with an estimated completion date of 2024. Neo-AEGIS is comparing the older ECF regimen (epirubicin/cisplatin/5-FU) as used in the MAGIC trials versus neoadjuvant CRT given as per the CROSS regimen (NCT01726452), and is also expected to complete in 2024. The TOPGEAR trial (NCT01924819), which is more of a gastric study but junctional cancers are allowed, is evaluating the perioperative MAGIC ECF regimen alone versus with the addition of preoperative CRT. Finally, the JCOG1109, NExT study[25] is assessing a number of strategies for locally advanced ESCCs, including 2 different chemotherapy regimens and 1 CRT regimen (ie, preoperative cisplatin/5-FU vs preoperative

Table 1. Pivotal Trials in Localized Esophageal/Gastroesophageal Junction Cancer

Trial	Study Arms	Outcomes
RTOG 8911[12]	Surgery vs CF × 3 → surgery	Median OS, 16.1 vs 14.9 mo.; HR, 1.07; 95% CI, 0.87–1.32; *P*=.53
SWOG-9008/INT-0116[13]	Surgery vs surgery → CRT	3-y OS rate, 41% vs 50%; HR, 1.35; 95% CI, 1.09–1.66; *P*=.005
OE02[14]	Surgery vs CF × 2 → surgery	Median OS, 13.3 vs 16.8 mo.; HR, 0.79; 95% CI, 0.67–0.93; *P*=.004
MAGIC[15]	Surgery vs ECF × 3 → surgery → ECF × 3	5-y OS rate, 23.0% vs 36.3%; HR, 0.75; 95% CI, 0.60–0.93; *P*=.009
POET[16,17]	Induction chemo → surgery vs induction chemo → CRT → surgery	3-y OS rate, 27.7% vs 47.7%; *P*=.07; study closed early due to poor accrual
FNCLCC/FFCD[18]	Surgery vs CF × 3 → surgery → CF × 3	5-y OS rate, 24.0% vs 38%; HR, 0.69; 95% CI, 0.50–0.95; *P*=.02
CROSS[7]	Surgery vs CRT (+ carboplatin/paclitaxel) → surgery	Median OS, 24.0 vs 49.4 mo.; HR, 0.657; 95% CI, 0.495–0.871; *P*=.003
NeoRes[19]	Chemo → surgery vs CRT → surgery	3-y OS rate, 49% vs 47%; *P*=.77
FLOT4-AIO[20]	FLOT × 4 → surgery → FLOT × 4 vs ECF × 4 → surgery → ECF × 3	5-y OS rate, 45% vs 36%; HR, 0.77; 95% CI, 0.63–0.94; *P*=.012
OE05[21]	CF x 2 → surgery vs ECX × 4 → surgery	Median OS, 23.4 vs 26.1 mo.; HR, 0.90; 95% CI, 0.77–1.05; *P*=.19
ST03[22]	(ECX + bevacizumab) × 3 → surgery → (ECX + bevacizumab) × 3 vs ECX × 3 → surgery → ECX × 3	3-y OS rate, 48.1% vs 50.3%; HR, 1.09; 95% CI, 0.91–1.29; *P*=.36

Abbreviations: CF, cisplatin/5-FU; chemo, chemotherapy; CRT, chemoradiotherapy; ECF, epirubicin/cisplatin/5-FU; ECX, epirubicin/cisplatin/capecitabine; FLOT, 5-FU/leucovorin/oxaliplatin/docetaxel; HR, hazard ratio; OS, overall survival.

docetaxel/cisplatin/5-FU vs cisplatin/5-FU + radiotherapy). In total, 501 patients will be accrued from 41 Japanese institutions.

Emerging Targeted Therapy Approaches

An eagerly awaited study, which completed enrollment but had not been presented at the time of writing, is the phase III RTOG-1010 trial (ClinicalTrials.gov identifier: NCT01196390) evaluating the addition of trastuzumab to trimodality therapy in HER2-overexpressing esophageal and GEJ adenocarcinomas. This study commenced in December 2010 and has enrolled 591 participants with stage IB–IIIB esophageal cancer as staged by the 7th edition of the AJCC Cancer Staging Manual. Patients are treated with the CROSS chemotherapy regimen of weekly paclitaxel/carboplatin either alone or in addition to trastuzumab weekly for 7 doses before surgery and, beginning 21 to 56 days after esophagectomy, every 3 weeks for 13 cycles in the absence of disease progression or unacceptable toxicity. In the metastatic setting, chemotherapy + trastuzumab is standard of care in the 15% to 20% of patients with HER2-positive disease. It will be interesting to see whether this approach is safe in the neoadjuvant setting when combined with radiotherapy and whether it results in improvement of the primary endpoint of DFS. Secondary endpoints include pathologic complete response (pCR), OS, safety, and quality of life.

Emerging Immunotherapy Approaches

Increasing data show that histology is important in esophageal cancer, with ESCC being slightly more sensitive to PD-1 inhibition than EAC. This may have implications for multimodality treatment of ESCC and EAC, but very limited data are currently available in operable disease. In the metastatic setting, the phase II KEYNOTE-180 study investigated the efficacy of pembrolizumab in heavily pretreated PD-L1–positive ESCC and showed an objective response rate of 14.3%.[26] Similarly, nivolumab, 3 mg/kg every 2 weeks in the phase II single-arm Japanese ONO-4538 study (n=65) resulted in an objective response rate of 17.2%[27]; median OS was 12.1 months and 14% of patients experienced serious adverse events, but there were no treatment-related deaths. Formal publication of the large phase III trials in the second-line metastatic ESCC setting is awaited, including KEYNOTE-181[28] and ATTRACTION-3,[29] which assessed the efficacy of both pembrolizumab and nivolumab, respectively.

A recent press release confirmed that ATTRACTION-3 comparing nivolumab with chemotherapy (docetaxel or paclitaxel) in patients with PD-L1–unselected, unresectable, or recurrent esophageal cancer who were refractory to or intolerant of combination therapy with a platinum/fluoropyrimidine, has met its primary endpoint of improving OS.[29] Data from KEYNOTE-181 were presented in January 2019,[28] which randomized patients with advanced/metastatic ESCC and EAC to either pembrolizumab (200 mg every 3 weeks) or chemotherapy (docetaxel, 75 mg/m^2 every 3 weeks, or paclitaxel, 80–100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, or irinotecan 80 mg/m^2 on day 1 every 14 days). OS was superior in the pembrolizumab arm in patients whose tumors had a PD-L1 combined positive score of ≥10. Although not statistically significant, a better response to pembrolizumab was seen

in patients with ESCC versus EAC. Implications of the results of these studies in stage II/III esophageal cancer remain to be determined, but ongoing studies, including the adjuvant CheckMate 577 trial (ClinicalTrials.gov identifier: NCT02743494), will help determine whether ESCC is more sensitive to single-agent PD-1 blockade than EAC.

What is clear, however, is that a more comprehensive understanding of the immune microenvironment will be needed to select the optimal immunotherapeutic approaches in early-stage esophageal cancer. PD-L1 expression occurs in approximately 40% of esophageal cancers[30–32]; however, this is a dynamic biomarker and can be upregulated as a result of chemotherapy and radiotherapy in early-stage disease. It is unknown whether the hypothetical synergy that should exist when combining PD-1 inhibitors with CRT will result in improved patient outcomes. Mismatch repair deficiency and Epstein-Barr virus infection, which increase PD-L1 expression in gastric cancer, are not seen in esophageal cancer.[33,34] IFN-γ signature scores and an 18-gene T-cell inflamed gene expression signature to try to enrich a patient population more likely to experience treatment response have had mixed results.[35,36] To date, no clinically validated biomarkers can identify prospectively likely responders from nonresponders. The hope is that data from the large ongoing studies in operable esophageal cancer will improve understanding.

PD-1 Inhibition in Operable Esophageal Cancer

A number of important global phase III trials are currently enrolling patients to determine whether addition of PD-1/PD-L1 inhibitors to CRT or to chemotherapy alone before surgery or their use as single agents in the adjuvant setting can improve survival in patients with stage II/III esophageal cancer (Table 2). The underlying hypothesis behind these trials is that combination chemotherapy/immunotherapy will act synergistically to decrease tumor burden, improve complete resection rates, eliminate micrometastatic disease, and increase pCR, which is a surrogate of long-term survival.[37]

CheckMate 577 (ClinicalTrials.gov identifier: NCT02743494) is studying adjuvant nivolumab in patients with resected lower esophageal/GEJ cancer.[38] In total, 760 patients will be randomized 2:1 to either nivolumab, 240 mg intravenously every 2 weeks for 16 weeks then 480 mg every 4 weeks for a maximum of 12 months or placebo. The window for enrollment is 4 to 16 weeks postresection, and the study will complete enrollment in 2019. Primary endpoints are OS and DFS.

Currently, there are a lack of data to guide medical oncologists regarding how to manage patients who have received trimodality therapy but whose postoperative surgical pathology report shows lymph node–positive disease. Many oncologists feel the need to give additional chemotherapy, but this approach is not supported by evidence-based medicine. The hope is that CheckMate 577 will help answer some of these questions, but because it is an adjuvant study, it will be a few years before results on efficacy endpoints are available.

KEYNOTE-585 (ClinicalTrials.gov identifier: NCT03221426) is a phase III study of perioperative chemotherapy (cisplatin, 80 mg/m^2 every 3 weeks + 5-FU [FP] via continuous infusion on days 1–5 every 3 weeks or cisplatin + capecitabine [XP], 1,000 mg/m^2 orally twice daily on days 1–14 every 3 weeks as per investigators choice) plus pembrolizumab

Table 2. Ongoing Trials Investigating HER2-Targeted Agents or Checkpoint Inhibitors

Target	Immune Checkpoint Inhibitor/Targeted Therapy	Adjuvant or Neoadjuvant Setting (ClinicalTrials.gov Identifier)
PD-1	Nivolumab	CheckMate 577 (phase III) Nivolumab vs placebo in resected stage II/III esophageal/GEJ carcinomas (NCT02743494)
PD-1	Pembrolizumab	KEYNOTE-585 (phase III) Perioperative chemotherapy (cisplatin/5-FU or cisplatin/capecitabine as per investigators choice or FLOT for 4 administrations) + pembrolizumab in operable gastric or GEJ adenocarcinoma (NCT03221426)
PD-L1	Atezolizumab	DANTE (phase II) Atezolizumab + FLOT vs FLOT in operable gastric or GEJ adenocarcinoma (NCT03421288)
PD-1 and CTLA-4	Nivolumab and ipilimumab	ECOG/ACRIN EA2714 (phase II) Perioperative nivolumab and ipilimumab in addition to standard-of-care chemoradiotherapy in operable esophageal and GEJ cancer (NCT03604991)
HER2	Trastuzumab	RTOG-1010 (phase III) Trastuzumab in combination with paclitaxel/carboplatin and radiotherapy in HER2-positive esophageal and GEJ adenocarcinoma (NCT01196390)

Abbreviations: FLOT, 5-FU/leucovorin/oxaliplatin/docetaxel; GEJ, gastroesophageal junction.

(200 mg intravenously every 3 weeks) in patients with previously untreated, localized, resectable GEJ or gastric cancer.[39] This study commenced in late 2017 and completion is estimated in July 2023. Initially, the trial design was to evaluate the previously listed chemotherapy regimens, but because FLOT4-AIO,[40] consisting of docetaxel, oxaliplatin, 5-FU, and leucovorin, was a positive trial, a separate safety cohort to evaluate FLOT + pembrolizumab was added. If shown to be safe, this regimen will be added as one of the chemotherapy regimens to be assessed in the main study. In total, 860 patients will be randomized to 3 cycles of neoadjuvant chemotherapy plus either pembrolizumab or placebo followed by surgery, and then in the adjuvant setting to an additional 3 cycles of either XP or FP or FLOT ± pembrolizumab followed by 11 cycles of either pembrolizumab or placebo as per the prior double-blind randomization.

The smaller randomized, open-label, phase II DANTE trial (ClinicalTrials.gov identifier: NCT03421288) is currently assessing the efficacy and safety of atezolizumab + FLOT versus FLOT alone in patients with GEJ and gastric adenocarcinoma. The primary outcome is to compare DFS/progression-free survival between arms. This study commenced in 2018 with an estimated enrollment of 295 patients, and completion is scheduled for 2025. Patients are randomized to receive atezolizumab (840 mg intravenously over 1 hour) + FLOT (docetaxel, 50 mg/m^2, day 1; oxaliplatin, 85 mg/m^2, day 1; calcium folinate, 200 mg/m^2 day 1; 5-FU, 2,600 mg/m^2 day 1) in 4 two-week treatment cycles before undergoing surgery. After surgery, patients will receive 4 additional 2-week cycles of atezolizumab + FLOT followed by 8 additional 3-week treatment cycles with atezolizumab alone (maintenance setting, 1,200 mg every 3 weeks). In the event of chemotherapy-related toxicity, FLOT can be deescalated to 5-FU/leucovorin/oxaliplatin, 5-FU/leucovorin/docetaxel, or 5-FU/leucovorin at any time and at the investigator's discretion.

Neoadjuvant approaches combining PD-1 inhibitors with CRT before esophagectomy are being investigated. Preliminary reports in esophageal cancer suggest that stromal PD-L1 expression increases from approximately 45.16% before neoadjuvant therapy to 77.42% expression after neoadjuvant CRT,[41,42] with a comparison of CD8$^+$ T cells in paired pre-neoadjuvant and post-neoadjuvant therapy showing a mean increase of 5.5 CD8$^+$ T cells/100 tumor cells (P=.02). Results were recently presented of the small CheckMate 906 study (n=32; ClinicalTrials.gov identifier: NCT03044613), which assessed the safety/feasibility of 2 cycles of induction nivolumab every 2 weeks before standard-of-care carboplatin/paclitaxel/radiotherapy plus 3 additional cycles of nivolumab at week 1, 3, and 5 of CRT.[43] Combination CRT + nivolumab had limited side effects with no incidences of pneumonitis, did not result in surgical delay or enhanced surgical morbidity/mortality, and induced a pCR rate of 31% in stage II/III esophageal/GEJ cancers. Interesting temporal dynamics of T-cell receptor clonotypes were identified, but additional data in a larger study are needed. ECOG recently opened the phase II/III EA2174 study (NCT03604991) investigating the efficacy of perioperative nivolumab and ipilimumab in 278 patients with locoregional esophageal or GEJ adenocarcinoma. Primary endpoints are an assessment of the pCR rate and DFS, with study completion estimated in 2023.

Conclusions

Esophageal cancer requires a multimodality treatment approach perhaps more than any other solid tumor, but unfortunately, treatment advances have been slow and incremental at best, with survival rates not improving dramatically in the past 5 to 10 years. Centralizing treatment in centers of excellence, specifically the surgical component of care, is improving postoperative morbidity and mortality. Advances in systemic and radiation therapy have been minimal, but data from the ESOPEC, Neo-AEGIS, TOPGEAR, and NExT studies are awaited to finally demonstrate whether the neoadjuvant CRT approach is better than perioperative chemotherapy. Data from RTOG-1010 should help determine whether targeted therapy with trastuzumab can be moved from the metastatic setting to use in operable HER2-positive tumors when combined with CRT. Finally, results from a large number of immunotherapy trials, both in the adjuvant and neoadjuvant setting, in stage II/III disease will help determine how to best target the immune microenvironment of these heterogenous tumors. What is very clear is that the diversity of clinical outcomes seen in patients with similar stages of esophageal cancer cannot be explained by molecular heterogeneity alone. A much more comprehensive analysis of the underlying immune microenvironment is required to make progress in this difficult-to-treat disease.

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