Management of Locally Advanced Esophageal Cancer

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KEYWORDS

• Esophageal cancer • Adenocarcinoma • Squamous cell carcinoma
• Chemoradiation • Salvage • MSI • PD-L1 • HER2

KEY POINTS

- Trimodality therapy should be preferred over bimodality therapy as the gold standard for locally advanced esophageal cancers in patients who are candidates.
- Chemoradiation or chemotherapy before esophagectomy provides better oncologic outcomes and improves overall survival compared with surgery alone.
- Hybrid or minimally invasive esophagectomy should be considered in appropriate patients.
- In patients with unresectable or metastatic disease, novel therapies should be considered for tumor profiles positive for HER2, MSI-H/dMMR, and PD-L1 positive.

BACKGROUND

Esophageal cancer is one of the most common causes of cancer deaths worldwide. However, in the United States and other western societies, it is a relatively uncommon disease. In the United States, esophageal cancer represented 17,650 (1%) of diagnosed tumors, and 16,080 (2.6%) of cancer deaths in 2019.[1] From 2007 to 2016, localized disease accounted for 20% of cases compared with 32% with regional involvement.[2] Most cases are advanced beyond local disease at time of diagnosis, due to the insidious onset of symptoms. Upward of 90% of patients present with dysphagia, secondary to progressive obstruction of the esophageal lumen. Other symptoms include weight loss, odynophagia, emesis, cough, regurgitation, anemia, hematemesis, and aspiration pneumonia.

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Surg Oncol Clin N Am 29 (2020) 631–646
https://doi.org/10.1016/j.soc.2020.06.003
surgonc.theclinics.com

The current range of therapies differs based on stage, histology, and performance status of the patient. While early, intramucosal disease can be locally controlled and potentially cured through endoscopic resection techniques, tumor invasion into or beyond the deep submucosa has considerable risk of lymphatic involvement, often necessitating a multimodality approach for treatments. For example, in a study of 90 patients with superficial esophageal adenocarcinoma (EAC), tumor confinement to the lamina propria had 0% lymphatic invasion, while tumors with deep submucosal involvement had 36% regional lymph node metastasis on surgical pathology.[3] More advanced stages with nodal involvement portends a poor prognosis in esophageal cancer with a 5-year overall survival (OS) of 25% in those with regional disease compared with 47% in patients with localized disease.[2]

Upfront esophagectomy was common in the past, but evidence has accumulated that this approach does not achieve cure in most locally advanced cases. Several studies have demonstrated significant benefits with a multimodality approach. Chemotherapy followed by surgery, trimodality with neoadjuvant chemoradiation followed by surgery, and bimodality therapy with definitive chemoradiation have all shown efficacy in randomized controlled trials. However, there are nuances to the findings of these studies. For patients in whom surgical resection is not an option, there are some completed studies and other ongoing trials exploring the benefit of HER2 targeted therapy and immune checkpoint inhibitors (ICI) in select patients. This article describes the current trends and controversies in the management of locally advanced esophageal cancer, and provides insight into optimal treatment strategies based on available evidence.

DEFINITION OF LOCALLY ADVANCED

For the purposes of this discussion, the definition of locally advanced disease will mainly include patients with disease that is resectable, lacks metastasis, but is beyond the superficial layers of the esophagus. According to the 8th edition of the AJCC/UICC staging manual,[4] this would include more advanced cT2N0 and cT3-4aN0-3M0. Tumors clinically staged cT2N0 fall into an intermediate stage, where some smaller tumors that are well to moderately differentiated and lack lymphovascular invasion (LVI) would be considered for upfront surgery. While others who have poor prognostic features, such as longer length (3.5 cm), poor differentiation, or LVI would typically be considered locally advanced and candidates for multimodality therapy based on risk of lymph node metastasis.[5]

SURGICAL APPROACHES FOR ESOPHAGECTOMY

Comparisons of transhiatal versus transthoracic approaches for esophagectomy have been extensively discussed within the literature.[6–9] Our institutional preference for locally advanced esophageal cancer is a transthoracic Ivor Lewis approach for several reasons. First, this affords direct visualization of the involved esophagus, which by definition has significant depth of tumor invasion and/or associated lymphadenopathy. Given the improved exposure, the likelihood of an R1/R2 resection may be reduced compared with a transhiatal approach.[10] In addition, an extensive lymphadenectomy can be performed for not only staging purposes, but also to provide excellent locoregional control of the disease which may translate into improved survival.[10] Moreover, the historically significant morbidity of an intrathoracic anastomotic leak with associated mediastinitis has been cited as a considerable disadvantage when compared with the relatively low risk of a cervical leak. However, surgical techniques, such as pedicled omental flaps have mitigated much of the risk associated with an

intrathoracic leak. Rescue strategies, including an endovacuum sponge, covered stents, and thoracoscopic or percutaneous chest drainage have also facilitated the management of perioperative conduit leaks.[11–19] Finally, enhanced recovery pathways, minimally invasive surgery, and multimodal analgesic regimens may further reduce the pulmonary morbidity associated with a transthoracic approach.[20,21]

In recent years, several studies have been published regarding minimally invasive esophagectomy (MIE). This surgical experience primarily focuses on either complete MIE, using conventional laparoscopy/thoracoscopy or robotic-assisted surgery, or a hybrid approach with laparoscopy combined with an open thoracotomy. Although our discussion centers on the aforementioned techniques, we should note that additional variations have been described, such as robotic-assisted transhiatal esophagectomy, and so forth.[22] Studies to date suggest that any form of MIE performed in selected patients is associated with fewer complications, less pain, and reduced lengths of stay with equivalent oncologic outcomes as compared with open esophagectomy.[23–26] In addition, in a major multicenter randomized controlled trial comparing hybrid Ivor Lewis esophagectomy with open surgery, Mariette and colleagues[27] found that a hybrid approach was associated with a 77% reduction in the rate of major intraoperative and postoperative complications compared with open esophagectomy. This decrease in overall complications was in large part attributed to a 50% reduction in pulmonary complications in the hybrid group. We should note that the definition of a major complication included Clavien-Dindo grade II or higher events. Given the broad range of this definition, the sequelae of these complications to patients in this study encompasses a wide range of outcomes. There were no differences between cohorts in the number of lymph nodes resected or surgical margin positivity. In addition, 3-year OS was 67% in the hybrid group compared with 55% in the open group, although this difference did not reach statistical significance.[27] Considering the potential for lower morbidity reported within the literature, MIE or hybrid esophagectomy may be associated with improved perioperative outcomes in centers with experience in using these approaches.

NEOADJUVANT CHEMOTHERAPY

Due to the difficulty of patients tolerating adjuvant chemotherapy and rather disappointing outcomes with upfront surgery in patients with locally advanced disease, much of the attention has been shifted to neoadjuvant therapies. Early trials comparing neoadjuvant chemotherapy plus surgery with surgery alone have reported mixed results, with the European MRC trial showing survival benefit in the neoadjuvant chemotherapy group at both 2 years[28] (43% versus 34%) and 5 years[29] (23% versus 17%; $P = .03$), while the US Intergroup-113 trial[30,31] showed no difference in 2- or 5-year survival. In a meta-analysis of 8 trials comparing neoadjuvant chemotherapy versus surgery alone, there was a significant 2-year OS benefit of 7% (hazard ratio [HR] = 0.90; 95% CI, 0.81–1.00; $P = .05$) in the neoadjuvant chemotherapy group. By histology, the benefit appears to be significant for EAC (HR = 0.78; 95% CI, 0.64–0.95; $P = .014$), but not esophageal squamous cell carcinoma (ESCC). The benefit of neoadjuvant chemotherapy has also been observed in large trials, including MAGIC[32] and ACCORD,[33] where 26% and 75% of the tumors, respectively, are located in the lower esophagus or gastroesophageal junction (GEJ). Recent data on neoadjuvant chemotherapy regimen consisting of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) have also shown promising results, where 30% of patients with GEJ EAC had pathologic complete response (pCR: ypT0N0M0) upon resection[34] and

up to 78% of patients achieved 2-year survival.[35] These trials have focused on EAC of the lower esophagus and GEJ, and results should not be extrapolated to ESCC.

TRIMODALITY THERAPY

In one of the most referenced studies, the CROSS trial[36] evaluated 366 patients (75% EAC and 22% ESCC) comparing neoadjuvant chemotherapy followed by surgery versus surgery alone. Neoadjuvant chemotherapy consisted of 5 cycles of intravenous carboplatin and paclitaxel with concurrent radiation (41.4 Gy in 23 fractions) followed by esophagectomy within 4 to 6 weeks after chemoradiation. With a medium follow-up period of 45 months, the chemoradiation plus surgery group had a higher proportion of OS compared with those who had surgery alone (49.4% versus 24%; $P = .003$). In addition, patients who underwent neoadjuvant chemoradiation had a sustained reduction in both locoregional disease (22% versus 38%; $P<.001$) and distant disease recurrences (49% versus 66%; $P = .004$). An R0 resection was achieved in 92% of the chemoradiation–surgery group compared with 69% in the surgery-only group ($P<.001$). pCR was observed in 23% of the EAC and 49% of the ESCC. While the number of nodes resected was not different between the 2 groups, 75% of the patients in the surgery-only group had positive nodes compared with 31% in the chemoradiation–surgery group ($P<.001$). These results were echoed by the NEO-CRTEC 20150 trial,[37] where 451 ESCC cases were evaluated. There was an improved OS in the neoadjuvant group (100 versus 67 months; $P = .025$), a higher rate of R0 resections, and a 43.2% pCR rate. These 2 large trials showed the benefit of trimodality therapy in both EAC and ESCC, and the results suggest that chemoradiation before surgery offers not only a survival benefit for patients, but results in more frequent R0 resection compared with upfront surgery. Currently, trimodality therapy consisting of neoadjuvant chemoradiation followed by surgery or chemotherapy followed by surgery should be the standard of care in locally advanced esophageal carcinomas.

NEOADJUVANT CHEMOTHERAPY VERSUS NEOADJUVANT CHEMORADIATION

The decision of neoadjuvant chemotherapy or chemoradiation is a topic for debate as available trial data are still inconclusive. The POET trial[38] evaluated neoadjuvant chemotherapy versus neoadjuvant chemoradiation in locally advanced GEJ EAC. Neoadjuvant chemoradiation showed an improved pCR and tumor-free lymph nodes. Despite not being statistically significant, there was a survival benefit at 3 years in the chemoradiation group (47.4% versus 27.7%; $P = .07$). The NeoRes trial[39] compared the 2 neoadjuvant treatments in both EAC and ESCC. While the chemoradiation group had better pCR (28% versus 9%; $P = .002$), lower lymph node disease, and better R0 resection, there were no differences in OS. It is important to note that, in this trial, both EAC and ESCC were included, and may have diluted the benefit of a particular neoadjuvant modality for a specific histologic type. Another important consideration is the method of achieving locoregional control. NeoRes had a higher rate of 2- or 3-field approach compared with POET or CROSS, potentially negating the benefit of radiation in locoregional control. In patients who could not tolerate such an approach, perhaps radiation helps to obtain locoregional control. Nevertheless, it is important to distinguish which patient population would benefit from neoadjuvant chemotherapy versus chemoradiation. Currently there are 2 ongoing clinical trials—ESOPEC[40] using the FLOT protocol, and NEO-AEGIS[41] using the MAGIC or FLOT protocol in comparison with the neoadjuvant chemoradiation protocol used in the CROSS trial to evaluate survival, morbidity and quality of life.

BIMODALITY THERAPY (DEFINITIVE CHEMORADIATION)

Although trimodality therapy offers improved survival and locoregional disease control, there are many who achieve pCR after chemoradiation, especially in ESCC. The value of surgery in these patients is controversial. While it is generally agreed upon that surgery should only be offered to selected patients, the optimal selection criteria are unclear. There are 2 studies that offer some support for bimodality therapy (definitive chemoradiation) versus trimodality therapy in patients with ESCC. A randomized trial by Stahl and colleagues[42] compared 172 patients in cohorts of planned surgery versus observation. After induction chemotherapy, trimodality patients were treated with neoadjuvant chemoradiation (40 Gy) followed by surgery, and bimodality patients completed their definitive chemoradiation (50–60 Gy). Patients had a median follow-up of 6 years. At 2 years, the median survival time for chemoradiation with surgery was 16.4 months compared with 14.9 months without surgery, and the authors did not find a difference in OS between the 2 groups (39.9% versus. 35.4%; test for equivalence $\delta = -0.15$, $P = .007$). They did, however, find a lower local disease recurrence rate in patients who completed trimodality therapy, as well as lower use of palliative procedures, such as dysphagia during follow-up. Criticisms of the study include inappropriate statistical method for the given conclusion,[43] an unusually high 11.3% in-hospital surgical mortality, and survival trend favoring surgery in the Kaplan-Meier curve after 2 years.

The FFCD 9102 study[44] also reported equivalence in the outcomes of these 2 treatment arms; survival analysis at 2 years for trimodality (33.6% $\pm$ 4.5%) and bimodality (39.8% $\pm$ 4.5%) showed no statistical difference in the intent-to-treat analysis, with median survival times of 17.7 and 19.3 months, respectively. In contrast to the Stahl trial, this trial design randomized only those with excellent clinical response to chemoradiation. In an analysis by Vincent and colleagues,[45] patients excluded from the FFCD 9102 trial due to no response to chemoradiation, but who subsequently underwent surgery, had equivalent OS to the trial patients. The message is that, for patients who achieve clinical response, outcomes may be equivocal, but for those who have no response, surgery is still an important component of treatment of ESCC. Long-term results have not been published on this trial, which would be important to see the maintenance of equipoise beyond 2 years for this treatment strategy.

Recent, retrospective data for bimodality and trimodality therapy have not reflected the conclusions of the 2 trials. Barbetta and colleagues[46] compared 124 bimodality and 108 trimodality patients with locally advanced ESCC. The analysis of 5-year OS in a propensity score-matched cohort showed OS of 45% (95% CI, 33–62) for trimodality therapy compared with 29% (95% CI, 18–49) in the bimodality group, with surgery being an independent predictor of survival. The study is limited in its retrospective nature, and selection bias is inherent in the 2 groups, even after matching for known variables. Nevertheless, this further suggests that surgery should not be dismissed as part of the decision-making process for ESCC after chemoradiation.

SELECTIVE SURGERY STRATEGY

With pCR observed in 23% of EAC[47] and 35%–49% of ESCC[37,42,47] from chemoradiation alone, efforts have been made to differentiate those who would benefit from an esophagectomy and those who would not with either histology. Hence, strategies of selective esophageal resection after chemoradiation have been used by many centers.

The phase II RTOG 0246[48] study by Swisher and colleagues was designed to assess the feasibility of a selective resection strategy. After chemoradiation with

fluorouracil and cisplatin along with 50.4 Gy radiation, patients are restaged to determine clinical complete response (cCR) or clinical noncomplete response. The study was designed to detect a survival of 77.5% or greater at 1 year in patients who underwent selective or salvage esophagectomy. Study sample consisted of 72% EAC, and more than 70% T3 or N1 disease. Out of 41 eligible patients, 37 completed chemoradiation, of the 21 patients who underwent selected surgery, 17 had residual disease, 3 had recurrent disease, and 1 due to personal choice after achieving cCR. The 1-year survival was 71%, and did not reach the 77.5% hypothesized. In the long-term follow-up,[48] the 5- and 7-year OS was 36.6% (95% CI, 22.3–51.0) and 31.7% (95% CI, 18.3–46.0), respectively. Important to this trial was that the decision to go to surgery was based on the surgeon's assessment of less than complete response. Of interest, albeit a small trial, the surgeon's decision to operate was always confirmed by a pathology report showing residual disease. Unmeasured variables that are observed by experienced esophageal surgeons should not be overlooked; the outcomes of mucosal biopsy and positron emission tomographic maximum standard uptake value cannot and should not be the sole determination of need for surgery. All patients completing bimodality therapy should be seen by a surgeon and discussed in a multidisciplinary setting.

Nonetheless, further study is warranted. The ongoing SANO trial is a phase III, multicenter stepped-wedge cluster randomized controlled trial.[49] Designed as a noninferiority trial, the study compares active surveillance versus planned esophagectomy in 300 patients with EAC or ESCC. After chemoradiation, patients undergo 2 rounds of assessment for cCR at 4 to 6 weeks and then at 10 to 14 weeks after the end of chemoradiation, as described in the Pre-SANO trial.[50] Patients with cCR after both rounds are randomized to surgery or active surveillance group. This trial is powered to detect noninferiority by no lower than 15% of the expected 67% survival at 3 years. There is much interest for the outcomes of this study in determining who would benefit from an esophagectomy after neoadjuvant chemoradiation.

SALVAGE ESOPHAGECTOMY

In patients who have completed definitive chemotherapy and experienced recurrence of disease, restaging and surgical evaluation is warranted. Salvage esophagectomy is a viable option for select patients who failed with locoregional recurrence, however, outcomes of salvage esophagectomy may differ depending on histology and timing of recurrence. There is no universally accepted definition for salvage esophagectomy, most published studies define salvage esophagectomy as either esophagectomy more than 90 days after the end of chemoradiation for persistent disease, or radiographic and clinical evidence of disease-free interval before recurrence of disease. In a meta-analysis by Faiz and colleagues,[51] comprising a total of 28 studies and 1076 patients who received a salvage esophagectomy, the pooled 3-year survival rate for salvage patients was at 39%. In our experience of comparing salvage esophagectomy with those who had planned trimodality therapy, salvage patients had a 3-year OS (48% versus 55%) and 5-year OS (32% versus 45%) that were comparable with the planned surgery cohort.[52] One-third of patients in both groups had postoperative complications, although salvage patients had significantly more postoperative blood transfusions and intensive care unit admissions. Overall, salvage esophagectomy for EAC has an acceptable outcome compared with trimodality therapy, and patients who failed bimodality therapy should be considered for a salvage esophagectomy.

For ESCC, outcomes after salvage may not be comparable with trimodality therapy. In our experience of evaluating 41 patients who were planned to undergo salvage esophagectomy and 35 patients who underwent actual salvage esophagectomy, there was a 90-day mortality of 9.8% versus 17.1%, respectively.[53] Postoperative events (a summation of major pulmonary events, cardiovascular complications, and clinically significant anastomotic leaks) occurred in 36.6% of planned salvage esophagectomies and 71.4% of actual salvage esophagectomies. Three-year OS was 73% for planned and 46% for salvage groups. These results are limited to a single-center experience, and we caution against drawing conclusions directly from these 2 groups as selection bias is inherent. Nevertheless, should bimodality fail with locoregional recurrence, patients may not achieve the same durable survival with salvage esophagectomy as they would in EAC.

Outcomes in salvage esophagectomy in ESCC also seem to differ based on whether it is performed for persistent or recurrent disease. Wang and colleagues[54] found that patients who underwent salvage esophagectomy for recurrent disease have an improved 3-year survival compared with those with persistent disease (56% versus 30%). Taniyama and colleagues[55] reported similar findings in their 5-year survival rates in recurrent versus persistent disease (47% versus 13%). These studies were limited to small sample size, lack of adjustment for confounders, and should be interpreted with caution. Nevertheless, this finding may indicate the aggressive nature of the underlying biology in persistent disease, and may play a role in the decision-making process for surgeons considering salvage esophagectomy.

SURVEILLANCE AFTER DEFINITIVE TREATMENT

Following locoregional control with either definitive chemoradiation or trimodality therapy, surveillance is a necessary component of long-term patient care. This is particularly true in the first 2 to 3 years after treatment as 80% to over 90% of recurrences occur during this time period.[56–58] In recently published data from 2 prospective phase II trials by the Swiss Group for Clinical Cancer Research, the median event-free survival time was 2.7 (95% CI, 1.9–6.8) years in patients undergoing trimodality therapy.[57] Viewed alternatively, data from a multi-institutional analysis reported the 5-year recurrence-free survival to be 54.9% in this patient population.[58] Both of these studies reported that pCR was significantly associated with not only recurrence-free survival, but OS as well.[57,58] However, regardless of tumor histoviability, surveillance is an important aspect of evaluating not only for recurrent disease, but for perioperative events, such as diaphragm hernia and metachronous cancers in the remnant esophagus.

Guidelines published by the National Comprehensive Cancer Network (NCCN) recommend that surveillance for patients with esophageal cancer should be dictated by both the stage of their disease and the type of definitive treatment administered.[59] In patients with T2-T4/N0-N3 disease treated with definitive chemoradiation, computed tomography of the chest and abdomen should be performed every 6 months for 2 years. In addition, because locoregional recurrences are frequently seen in these patients, an upper endoscopy should also be performed every 3 to 6 months for the first 2 years, followed by every 6 months in the third year, with clinical re-evaluation as required going forward. In some instances, patients with recurrent local disease may be candidates for salvage esophagectomy as discussed previously. In contrast, patients completing trimodality therapy do not require routine upper endoscopy surveillance due to the low incidence of local recurrence. Rather, these patients should undergo computed tomography of the chest and abdomen every

6 months for 2 years similar to bimodality patients. Beyond 2 years, both bimodality and trimodality patients should be imaged annually for at least 5 years after treatment.[59]

TARGETED THERAPY

When disease recurs and resection is not an option, tumor biology may provide targets for additional treatment options. HER2/neu is a tyrosine kinase receptor that acts as a growth factor. Its role is well understood in breast cancer, and HER2 is also prevalent in esophageal cancers. HER2-positive status is determined most commonly by a combination of immunohistochemistry (IHC) and fluorescent in situ hybridization.[60] Recently, next-generation sequencing has also been used to determine HER2 status in tumors with high concordance rate with the traditional system.[61] In available literature, approximately 15% to 32% of EAC,[62–65] and 2% to 11% of ESCC[62,63,66] overexpress HER2. HER2 portends a poor prognosis in breast cancer, but the prognostic value of HER2 is controversial in EAC; while some studies found HER2 to be prognostic for poor outcomes,[67–69] others find it to be a favorable prognosis.[65,70,71] Nevertheless, tyrosine kinase inhibitors targeting HER2 have been shown to prolong survival in esophagogastric adenocarcinoma.

The ToGA trial was a major phase III randomized control trial evaluating trastuzumab in addition to standard chemotherapy as first-line agent for treatment of HER2-positive advanced gastric or GEJ carcinomas. Patients with the addition of trastuzumab had longer OS than those who received chemotherapy alone (13.8 versus 11.1 months, HR = 0.74; 95% CI, 0.60–0.91, P = .0046), subgroup analysis showed those with higher HER2 positivity derived greater survival benefit from the treatment. Trastuzumab was approved by Food and Drug Administration (FDA), and the current NCCN guidelines[72] advocate for the addition of trastuzumab to chemotherapy as standard therapy for HER2-positive tumors in unresectable locally advanced, recurrent, or metastatic gastroesophageal adenocarcinoma where local therapy is not indicated.

IMMUNE CHECKPOINT INHIBITORS

Recent development of ICI targeting programmed death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway has shown promising results in patients who have exhausted standard therapies. PD-L1 positivity is determined by the so-called combined positive score (CPS), which is calculated as the number of PD-L1 expressing cells (tumor cells, lymphocytes, macrophages) divided by the total tumor cells, multiplied by 100. In most clinical trials, PD-L1 positivity is defined as CPS greater than 1 on IHC.[73–75] Pembrolizumab and nivolumab are the 2 anti-PD-1 antibody therapies that have been approved for use in the United States and Japan, respectively.

Results from the KEYNOTE-012[75] and KEYNOTE 059[76] trials granted FDA approval for the use of pembrolizumab for PD-L1-positive recurrent or metastatic esophagogastric junction (EGJ) adenocarcinomas. In Japan, nivolumab was approved for treatment of EGJ and gastric cancers regardless of PD-L1 status because of positive results from the ATTRACTION-2[77] study. In addition, a first-ever site-agnostic approval by the FDA was granted to pembrolizumab in 2017 to treat tumors expressing high microsatellite instability (MSI-H)/defective mismatch repair (dMMR),[78] therefore, MSI-H/dMMR status should also be determined in patients with metastatic disease or where local treatment is not feasible.

As second-line agents, ATTRACTION-3[79] phase III trial compared nivolumab to chemotherapy in 419 ESCC patients who were treatment refractory to previous

chemotherapy, and showed a better OS than the chemotherapy group (10.9 versus 8.4 months, $P = .019$). For pembrolizumab, the KEYNOTE-180[80] phase II trial evaluated 121 heavily pretreated patients; the objective response rate was 9.9% (95% CI, 5.2–16.7) and 13.8% (95% CI, 6.1–25.4) in PD-L1-positive patients. In the follow-up study, phase III KEYNOTE-181 trial,[81] 628 patients were randomized to either pembrolizumab or investigator choice of chemotherapy. Although there was no difference in OS in the cohort, pembrolizumab had a better safety profile than chemotherapy. Of importance, in patients with CPS $\geq$ 10, pembrolizumab demonstrated improved OS (9.3 versus 6.7 months, $P = .0074$). This led to the approval of pembrolizumab for previously treated, recurrent locally advanced or metastatic cancer in patients with CPS $\geq$ 10. The currently ongoing KEYNOTE-590 trial[82] (NCT03189719) will evaluate pembrolizumab plus chemotherapy as first-line therapy for locally advanced or metastatic esophageal cancer.

Although relatively new on the market, ICI seems to be providing select patients with durable responses who have no other treatment options. The nuances of incorporating immunotherapy into current treatment regimen will likely continue to evolve in the coming years. Regardless, ICI will likely become adopted due to observed survival benefit in these trials, and its safety profile in comparison with standard chemotherapy. At the least, it provides another tool in the armamentarium of treatment of esophageal cancers.

PALLIATION OF LOCALLY ADVANCED ESOPHAGEAL CANCER

In patients who are not candidates for definitive therapy, palliative care focuses primarily on symptom management. Patients with locoregionally advanced esophageal cancer suffer almost uniformly from dysphagia. Utilization of dysphagia grading scales may be helpful in classifying symptomology and assessing the response to treatment.[83] The degree of dysphagia often depends on the depth of tumor invasion at the time of diagnosis. In a study by Fang and colleagues,[84] a dysphagia grade of 3 or greater, indicating the ability to tolerate only liquids or those with complete dysphagia to liquids/saliva, had a positive predictive value of 100% for T3 disease, although sensitivity was only 36% in this study. Several different strategies have been used to address not only the inherent quality of life limitations from dysphagia, but also the malnutrition and weight loss that inevitably follow. First-line management of dysphagia in this patient population has traditionally been stenting.[85,86] Self-expanding metal stents (SEMS) are preferable to plastic stents and can typically be placed with minimal adverse events, with or without the use of fluoroscopy, and allow patients to swallow effectively immediately after procedure in most instances. Stent-related complications can occur and primarily include chest discomfort, migration of the stent, gastroesophageal reflux, or in rare cases esophageal perforation.[85,86] Long-term complications include the need for multiple stent exchanges and the possibility of fistula formation to the nearby airway. In our practice, we typically place partially covered SEMS, which prevents tumor ingrowth into the stent aiding future retrievability, while at the same time affording some granulation tissue within the stent's exposed metal flange to limit migration. Of note, in patients with significant dysphagia in whom future definitive surgical resection is planned, evidence suggests that stents may reduce the likelihood of an R0 resection and worsen both locoregional control and OS compared with patients not undergoing stent placement.[59,87,88] Consequently, stents should be avoided as a bridge to surgery, regardless of whether neoadjuvant chemoradiotherapy is planned, because of poorer oncologic outcomes.

In addition to stent placement, several other methods have been used to address dysphagia in this population. These primarily include chemotherapy, external radiation therapy, brachytherapy, photodynamic therapy, and laser or ablative therapy.[85,86,89] Aside from relieving dysphagia, surgeons should also consider the need for additional nutritional support with placement of feeding tubes. Percutaneous endoscopic gastrostomy tubes with bolus feedings are typically preferred to jejunostomy tubes in most patients.

Additional palliative considerations in this population include control of pain, chronic nausea, and psychosocial distress given the prognosis of their disease. The NCCN provides resources specific to these issues, which may be helpful in the management of these challenging situations. In addition, early involvement of supportive or palliative care services significantly aids in the management of both symptoms and discussions regarding goals of care.

SUMMARY

Treatment of locally advanced esophageal cancer requires a multimodality approach. Neoadjuvant chemotherapy or chemotherapy with concurrent radiation followed by surgery is the standard of care for both EAC and ESCC. In select patients who achieve cCR, definitive chemoradiation with close surveillance within the first 2 to 3 years is currently under scrutiny. Minimally invasive or hybrid approaches to esophagectomy show equivalent oncologic resection, while reducing perioperative risks, and should be considered. Patients with locoregional recurrences warrant a surgical evaluation for a salvage esophagectomy; however, in our experience, while morbidity and mortality seem equivalent for planned and salvage esophagectomy in EAC, salvage esophagectomy in ESCC shows a higher risk of major cardiopulmonary complications and significant anastomotic leaks. In patients with unresectable local disease or distal metastasis, tumor profiling can identify those who would benefit from novel targeted therapy and immunotherapy. Palliative goals for patients should be focused on symptomatic relief, mainly dysphagia, with an emphasis on early involvement in supportive care services to manage symptoms and discussion of goals of care.

DISCLOSURE

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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