Review

Current therapeutic approaches to localized carcinoma of the esophagus and gastroesophageal junction

Mariela A Blum*, Akihiro Suzuki¹, Takashi Taketa¹ & Jaffer A Ajani¹

Practice Points

- Two trials evaluated adjuvant radiation therapy (only) for localized resected esophageal cancer. There was no benefit for survival.
- There is tenuous evidence to suggest that adjuvant chemoradiation provides benefit; data are only available from patients with distal esophageal adenocarcinoma who have R₁ resection or positive nodal disease.
- There is no evidence for survival benefit of postoperative chemotherapy.
- Preoperative chemotherapy is an option in adenocarcinoma. This strategy provides weak evidence for survival advantage.
- Preoperative chemoradiation prior to surgery provides the strongest level 1 evidence for survival advantage.
- Definitive chemoradiation provides strong level 1 evidence for patients who are not eligible for trimodality therapy.
- Definitive chemoradiation is an option for esophageal squamous cell carcinoma.
- Induction chemotherapy prior to chemoradiation is a subject of further investigation.

SUMMARY  Esophageal cancer is a deadly disease and only 40–50% of patients have potentially resectable cancer at diagnosis. Accurate staging and multidisciplinary evaluation are essential before any therapy is started. In locally advanced disease, primary surgery leads to poor long-term survival; however, an R₀ resection is essential for cure. Clinical trials investigating multimodality treatments have led to improved outcomes and more options. However, the treatment of localized esophageal cancer based on two major histologic subtypes is a subject of debate. Squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC) are included in most of the trials but it may take time to propose different approaches.

¹University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Mail Stop 426, Houston, TX 77030, USA
*Author for correspondence: mblum1@madanderson.org
In 2008, approximately 482,300 new cases were diagnosed and 406,800 deaths occurred worldwide due to esophageal cancer (EC). EC represents one of the most deadly diseases [1]. In the USA, the incidence and mortality rates are similar, with 14,710 deaths owing to cancer of the esophagus in 2011 [101]. The median age at diagnosis is 68 years and EC is three- to four-times more common among men than women [101]. The most common histologic subtypes are squamous cell carcinoma (SCC; common in the endemic areas and often located in the middle or upper third of the esophagus) and esophageal adenocarcinoma (EAC; common in the west and often located in the lower esophagus and involving the gastroesophageal junction) [2]. SCC is associated with poor nutritional status, smoking and moderate to excessive alcohol consumption [3–5]. Conditions that cause an injury to the squamous mucosa (e.g., tylosis, Plummer Vinson syndrome and achalasia) predispose to SCC. Gastroesophageal reflux disease and obesity are associated with EAC [6]. Smoking may add to the risk of EAC in patients with Barrett’s esophagus [7]. Barrett’s esophagus is the only known premalignant condition that can lead to adenocarcinoma; however, the rate of conversion is <0.2% per year [8,9]. In this respect, Barrett’s esophagus might be a protective phenomenon with a low risk of malignant transformation. Nevertheless, the incidence of EAC in the west has increased 15—42% annually, with a 20.6% annual increase in the USA [10,11].

Staging
Accurate staging is important since it is central to establishing a therapeutic strategy and may influence prognosis. Initial diagnosis is confirmed by an upper endoscopy. Computed tomography is essential to assess if any metastatic disease exists. However, computed tomography has a sensitivity of 40–80% and specificity of 14–97% for correctly designating T stage and a sensitivity of 40–79% and specificity of 25–67% for the N stage [12]. Bronchoscopy should be considered to exclude airway invasion for cancers located at ≤25 cm from the incisors. 18-fluorodeoxyglucose PET is increasingly being used as an initial staging tool and can detect unsuspected metastatic disease in up to 15% of patients [13] and is complementary to computed tomography [14]. Recent reports suggest that PET can provide additional information regarding the depth of tumor invasion, lymph node metastasis and survival rates [15–17]. Endoscopic ultrasound with fine-needle aspiration provides another useful staging tool [12]. The sensitivity of the endoscopic ultrasound in the detection of nodal metastasis is 63–89% with a specificity of 75—81% [18,19].

Therapeutic strategies
LEC is defined as EC limited to the esophagus with or without regional nodal involvement [10]. There are several factors that influence survival in LEC patients: first, T and N categories; second, location of the primary tumor; third, comorbid conditions including age of the patient; fourth, geographic distribution of any involved nodes (e.g., nodes on both sides of the diaphragm); and last, sometimes, histology. The N designation in the new American Joint Committee on Cancer (AJCC) 7th staging is based on the number of lymph nodes rather than nodal stations [20].

Based on a large multi-institutional database of LEC, most patients have a T3 stage (51%) and EAC is the common histology (60%) (Table 1) [21]. The 5-year survival rates for patients with T1, T2, T3 and T4 tumors are 69, 51, 17 and...
0%, respectively [22]. The significant decrease in survival beyond T1a is due to nodal involvement. Overall 5-year survival decreased from 55% in N0 patients to 31% in patients with 1–2 positive nodes and 6–7% in those with 3 or more nodes involved [22,23].

Most studies have included patients with both EAC and SCC but these have different epidemiology, tumor biology and pathogenesis. Herein, we attempt to describe the management of these two entities separately. It may be that eventually the management will be entirely different.

**Endoscopic therapies**

- **Endoscopic mucosal resection**
  For early-stage EAC or SCC tumors (T1aN0M0 or TIS) confined to the mucosa, the management includes endoscopic mucosal resection (EMR) plus ablation with local control of 93–99% and 5-year disease-specific survival of 84–98% [24]. EMR provides accurate diagnostic information on invasion, depth, differentiation and lymphovascular invasion. Therefore, when EMR is not therapeutic, it is diagnostic. There is increasing emphasis on reducing piecemeal EMRs in favor of endoscopic submucosal dissection but not many gastroenterologists are trained to perform endoscopic submucosal dissection. Metachronus cancer (field effect) can occur, therefore surveillance endoscopy is recommended every 3–6 months for 1 year, and then annually for at least 5 years.

- **Photodynamic therapy**
  Photodynamic therapy uses a photosensitizer drug that concentrates in the dysplastic and malignant tissue; when laser light is applied, it activates the drug and results in a photochemical reaction that leads to selective tissue destruction. Photodynamic therapy can potentially eradicate early T1 cancers [25]. Up to 30% of patients may develop esophageal strictures or cutaneous photosensitivity. Photodynamic therapy is rarely used today.

- **Esophagectomy**
  Primary surgical resection is recommended for noncervical tumors and T1bN0 stage. Patients with >T1b stage should be offered combined modality therapy (see below). The risk of lymph node involvement is higher in T1b tumors with lymphovascular invasion (46%) [10]. The optimal surgical approach is controversial. Surgical methods include: transthiatalesophagectomy (abdominal and left cervical incision), transthoracic (Ivor–Lewis esophagectomy), abdominal and right thoracic incision, left thoracotomy and radical (en bloc) resection. A meta-analysis of 44 series of transhiatal surgery and Ivor–Lewis surgery established that both approaches were comparable with more postoperative complications with the transhiatal surgery. Transhiatalesophagectomy was associated with a higher incidence of anastomotic complications and recurrent laryngeal nerve injury (5-year overall survival: transhiatal 24% vs Ivor–Lewis 26%) [26]. Regardless of the approach, R0 resection improves the drug-free survival and cure rate [27]. Surgery should be performed in high-volume centers by high-volume surgeons to decrease mortality [28,29].

### Management of T1b–3N1–3,M0

- **Adenocarcinoma of the esophagus**
  Preoperative treatment has been used in order to improve resectability, local control and survival. Two preoperative approaches have been used in LEC: combination chemotherapy followed by surgery or chemoradiation followed by surgery. Chemoradiotherapy produces a higher rate of pathologic complete response (pathCR).
PathCR can be associated with improved survival and can help with esophageal preservation strategies [30].

- **Preoperative chemotherapy**
  Preoperative chemotherapy has been studied in several trials; some of these have conflicting reports. The Radiation Therapy Oncology Group (RTOG) Trial 8911 (USA Intergroup 113) compared three cycles of preoperative cisplatin and 5-fluorouracil followed by surgery to surgery alone. The long-term results did not confirm survival advantage from preoperative chemotherapy and R1 resections had an ominous prognosis [31]. Conversely, the Medical Research Council (MRC) trial (n = 802) showed that both disease-free survival and overall survival were significantly longer with the preoperative chemotherapy. However, these differences were quite modest with improvement in the 5-year survival rates of 6%. There was no survival advantage for EAC and SCC subgroups [32].

- **Perioperative chemotherapy**
  The MRC Adjuvant Gastric Infusional Chemotherapy trial compared either surgery alone or perioperative chemotherapy with epirubicin, cisplatin and fluorouracil plus surgery in 503 patients with mainly gastric cancer; however, approximately 20% of patients had distal EC (n = 73) or gastro-esophageal junction adenocarcinoma (n = 58) [33]. There was survival improvement from preoperative chemotherapy but surgical control was substandard. In a similar trial (the Fédération Nationale des Centres de Lutte Contre le Cancer ACCORD07-FFCD 9703), 224 patients with gastric and lower esophageal adenocarcinoma were randomized to preoperative chemotherapy versus surgery alone. Preoperative chemotherapy improved drug-free survival and overall survival in patients with resectable adenocarcinoma of the stomach and lower esophagus [34]. A meta-analysis suggested marginal but not meaningful benefit from preoperative chemotherapy [35].

  In summary, preoperative chemotherapy in LEC patients produces marginal survival advantage and is recommended in some European countries.

- **Preoperative chemoradiation**
  We will discuss preoperative chemoradiation jointly with the management of SCC since trials have included both histologies.

- **Postoperative chemotherapy**
  There is no benefit to postoperative adjuvant chemotherapy.

- **Adjuvant chemoradiation**
  Adjuvant chemoradiation is recommended for lower EAC patients with positive nodes who get primary surgery. This approach is based on the Intergroup 0116 trial, in which 20% of patients had gastroesophageal junction adenocarcinoma but evidence for this is tenuous [36].

- **Squamous cell carcinoma of the esophagus**
  Preoperative chemotherapy
  Several small, randomized trials have evaluated the preoperative chemotherapy strategy with most having enrolled only SCC. These are mainly underpowered trials (Table 2) [37–44]. In a meta-analysis, patients with SCC, receiving neoadjuvant chemotherapy did not have survival benefit [45]. Currently, there are no data to support preoperative chemotherapy as standard option in SCC of the esophagus.

  Preoperative chemoradiation (SCC & adenocarcinoma)
  Six randomized trials restricted only to SCC compared chemoradiation before surgery versus surgery alone. Radiotherapy doses and chemotherapy regimens vary but the most common drugs were cisplatin and fluorouracil [46–51]. There was no difference between the two arms but the trials were underpowered and have other drawbacks. A recent meta-analysis suggested benefit in overall survival with preoperative chemoradiation compared with surgery for SCC [52]. On the other hand, the CROSS trial’s subgroup analysis suggests considerable benefit for SCC (results below) [53].

  Four other meta-analyses have also favored preoperative chemoradiotherapy [45,54–56]; unfortunately, meta-analyses cannot form level 1 evidence. Several underpowered randomized trials (Table 3) [57–59] and nonrandomized trials document the feasibility of preoperative chemoradiation in SCC and adenocarcinoma [60–63]. Analysis of preoperative chemoradiotherapy studies found a significant benefit over surgery for both histologies: hazard ratio (HR): 0.84 (95% CI: 0.71–0.99; p = 0.04) for SCC and HR: 0.75 (95% CI: 0.59–0.95; p = 0.18) for EAC [45].
An Intergroup trial (CALGB 9781) assigned 56 patients (42 resectable adenocarcinoma and 14 SCC of the esophagus) to neoadjuvant chemoradiation followed by surgery or surgery alone. With a median follow-up of 6 years, a significant survival benefit was seen for the combined modality group (4.5 years compared with 1.8 years with surgery only; \( p = 0.02 \)). The 5-year survival was 39% for trimodality treatment patients versus 16% for surgery alone [64].

Results of the CROSS trial are worth elaborating; this large, multicenter, randomized Phase III trial compared preoperative chemoradiotherapy followed by surgery with surgery alone. Three hundred and sixty-eight patients with T2–3N0–1M0 EAC or SCC were randomized to weekly paclitaxel 50 mg/m² and carboplatin area under curve of 2 for 5 weeks with concurrent radiation or surgery. The reported R0 resection rate was 92.3% in the chemoradiation arm versus 69% in the surgery-only arm. The median survival of patients who received chemoradiation was 49 months, compared with 26 months for those who had surgery. The 3-year overall survival rate was superior in the chemoradiation arm: 59% in the CRT arm vs 48% in the surgery alone arm (HR:0.67; \( p = 0.003 \)) [33].

A Phase III trial compared preoperative chemotherapy versus chemoradiotherapy followed by surgery in patients with EAC. Due to low accrual, this study was closed early and statistical significance was not achieved; however, results point to a survival advantage for preoperative chemoradiotherapy [66].

Cytotoxics that are commonly combined with radiation include paclitaxel and carboplatin, cisplatin and a fluoropyrimidine, oxaliplatin and fluoropyrimidine, carboplatin and fluorouracil,

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Histology</th>
<th>Treatment</th>
<th>RR</th>
<th>MS (months)</th>
<th>Survival difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al. (1988)</td>
<td>39</td>
<td>SCC</td>
<td>CDDP + vindesine + bleomycin × two cycles prior to surgery and CDDP + vindesine after surgery</td>
<td>47%</td>
<td>20 vs 6.2†</td>
<td>NS</td>
</tr>
<tr>
<td>Nygaard et al. (1992)</td>
<td>186</td>
<td>SCC</td>
<td>Group 1: Surgery alone</td>
<td>NR</td>
<td>7</td>
<td>NS between group 1 and 2</td>
</tr>
<tr>
<td>Schlag (1992)</td>
<td>46</td>
<td>SCC</td>
<td>CDDP + 5-FU + surgery</td>
<td>50%</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Maipang et al. (1994)</td>
<td>24</td>
<td>SCC</td>
<td>CDDP + bleomycin + vinblastine + surgery</td>
<td>53%</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Kok et al. (1997)</td>
<td>161</td>
<td>SCC</td>
<td>CDDP + VP-16 × two cycles + surgery</td>
<td>36%</td>
<td>18.5</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>Law et al. (1997)</td>
<td>147</td>
<td>SCC</td>
<td>CDDP + 5-FU + surgery</td>
<td>58%</td>
<td>16.8</td>
<td>OS improved after 3–5 years</td>
</tr>
<tr>
<td>Baba et al. (2000)</td>
<td>42</td>
<td>SCC</td>
<td>5-FU + LV × two cycles + surgery</td>
<td>60%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ancona et al. (2001)</td>
<td>96</td>
<td>SCC</td>
<td>CDDP + 5-FU + surgery</td>
<td>40%</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Stilidi et al. (2006)</td>
<td>78</td>
<td>SCC</td>
<td>CDDP + VP-16 + LV + 5-FU + surgery</td>
<td>68%</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Kelsen et al. (2007); (1998)</td>
<td>463</td>
<td>SCC  adenoca</td>
<td>CDDP + 5-FU × three cycles + surgery followed by CDDP + 5-FU × two surgery</td>
<td>19%</td>
<td>14.9</td>
<td>NS</td>
</tr>
<tr>
<td>MRC (2002)</td>
<td>802</td>
<td>SCC  adenoca</td>
<td>CDDP + 5-FU + surgery</td>
<td>37%</td>
<td>16.8</td>
<td>p = 0.004</td>
</tr>
</tbody>
</table>

†Nonresponders to chemotherapy.
5-FU: 5-Fluorouracil; Adenoca: Adenocarcinoma; CDDP: Cisplatin; LV: Leucovorin; MRC: Medical Research Council; MS: Median survival; NR: Not reported; NS: No survival difference; OS: Overall survival; RR: Relative risk; RT: Radiotherapy; SCC: Squamous cell carcinoma; VP-16: Etoposide.
and docetaxel and fluoropyrimidine. We recommend the use of two cytotoxics rather than one when feasible. Close monitoring and support of patients undergoing chemoradiation therapy is essential.

### Definitive chemoradiation therapy

The benefit of definitive chemoradiation over radiation alone was demonstrated by the Phase III RTOG 85-01 trial [66]. However, the subsequent Intergroup INT-0123 trial failed to document benefit of increase in the radiation dose to 64.8 Gy compared with 50.4 Gy [67]. Thus, doses higher than 50.4 Gy are not recommended. Intensity-modulated radiation therapy is preferred over 3D planning.

Two small Phase III trials have demonstrated the benefit of definitive chemoradiation versus preoperative chemotherapy in SCC. Stahl et al. randomized 172 patients with locally advanced SCC to induction chemotherapy followed by chemoradiotherapy and then surgery versus same regimen without surgery [68]. Overall survival was equivalent between the two arms (p < 0.05). Bedenne et al. also reported that esophagectomy confers no additional benefit to patients with SCC that had responded to initial chemoradiation [69]. These data support definitive chemoradiation in patients with SCC that respond to treatment.

If possible, salvage surgery is recommended for patients with recurrent or residual disease.
Adjuvant therapy
There is no benefit from adjuvant chemoradiation for patients with SCC.

Conclusion & future perspective
We face considerable challenges in managing patients with LEC. It is clear that the empiric approaches that are so prevalent today lead to unanticipated outcomes. This is due to considerable heterogeneity that exists in these tumors. We need to focus on sophisticated imaging and addressing the molecular biology of these tumors. One of the biomarkers that immediately available is the HER-2 protein. An RTOG trial is addressing Her-2 overexpressing cancers. The other challenge is to develop strategies for esophageal preservation. This strategy requires that we have a high pathCR rate and a predictive model for pathCR. Nevertheless, considerable progress has been made overall and the future appears bright.
LEC provides opportunities to cure the patient; however, therapy is associated with life-altering changes. We highly recommend that an experienced multidisciplinary team deals with these patients. When all therapies are delivered at a high-volume center, the results are more promising. Accurate and uniform staging is essential for a multidisciplinary team to provide a consensus recommendation. Primary surgery is discouraged except in T1bN0 patients. Endoscopic therapy for T1a (or high-grade dysplasia) should be offered but only by highly experienced endoscopists. The authors’ preference is preoperative chemoradiation over preoperative chemotherapy for lower EAC as part of the trimodality approach. However, preoperative chemotherapy is also an option. Definitive chemoradiation is recommended for patients who cannot withstand surgery or have an unresectable LEC and it is curative in some SCC patients. We must invest more to study sophisticated imaging, tumor biology and patient genetics to individualize therapy for each patient and move away from empiricism.

Financial & competing interests 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 manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

References
17 Suzuki A, Xiao L, Hayashi Y et al. Prognostic significance of baseline positron emission


Websites
