Surgical management of esophageal cancer

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Abstract: Esophageal cancer (EC) is an aggressive malignancy associated with an overall poor prognosis. The specific risk factors for EC vary by histologic type as well as geographic distribution but there is no widely applicable screening strategy to date. Patients can present with vague symptoms which can prove to be a diagnostic challenge. Furthermore, cases tend to present at a late stage, making therapeutic approach difficult. Despite ongoing changes in management strategy, surgery remains the only viable option for cure in early stage malignancy. Advances in operative and peri-operative management have led to a relatively safe and efficacious procedure that provides durable therapy. Additionally, careful consideration of procedure specific factors can help maximize patient benefit. This review focuses on the surgical approaches to the management of EC and highlights select current trends and recent advances.

Keywords: Esophageal cancer (EC); indications for surgery; surgical management; curative resection

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Introduction

Esophageal cancer (EC) is the 8th most common malignancy worldwide (1) with an estimated incidence of 456,000 new cases per year (2) and close to 17,000 cases in the US alone (3). Despite its relative infrequency, esophageal malignancy still remains a deadly disease with an overall 5-year survival of 18.7% (4) with the highest mortality rates occurring in Eastern Asia (14.1/100,000) (5). In the past 15 years, the management of EC has continued to evolve, however surgical resection remains the cornerstone of curative-intent treatment in early stage malignancy. While the histologic distribution of adenocarcinoma and squamous cell carcinoma can vary by risk factor and geographic location, the surgical management of both is essentially identical (6).

Clinical presentation

EC has been historically known as a difficult disease process to manage. The etiology may be multifactorial but a portion is owed to the unique presentation of this cancer. To date, no widely applicable screening methods for EC exist (7). In western nations, cancer screening and surveillance may be recommended for patients who are at high risk for Barrett's Esophagus and routine screening may be beneficial for those who are Caucasian, obese, male, or have long standing reflux symptoms (8). On the other hand, areas with high disease burden in rural China have benefited from a population based approach to endoscopic screening (9).

Additionally patient reported symptoms for EC can be vague, requiring engaged providers and at times extensive work-up before a final diagnosis is made. Presentation symptomatology spans from dysphagia and weight loss (74% and 57% respectively) to gastrointestinal reflux and dyspnea (20% and 12% respectively) (10). The unique anatomy of the esophagus can further contribute as the lack of a true serosa may add to the skewed distribution of cancer stage at initial presentation (up to 69% of patients already have regional and distant spread) (11).

Guiding principles to surgical management

The efficacious treatment of EC is complex. Following diagnosis, which is most commonly achieved via endoscopic biopsy, appropriate staging is paramount as it guides management decisions and indeed the decision to proceed with endoscopic therapy versus surgery versus induction chemotherapy/chemoradiation hinges on the clinical TNM stage (12,13). While locoregionally advanced (≥ T3 or N+) cancers tend to be treated with neoadjuvant chemoradiation therapy, selection for upfront surgery is important as patients with early cancers (≤ T2N0) are the most likely to benefit from operative intervention (14). The recent publication of the results of a phase III trial recapitulate this fact when investigators terminated the study after determining that neoadjuvant treatment, specifically in early cancers, was unlikely to result in a survival benefit when compared to surgery alone (15). Moreover, endoscopic therapy—which allows for organ preservation—has been shown to be effective for the treatment of intramucosal cancers (16,17). To this end, the pre-operative assessment of cancer extent proves crucial and routine inclusion of CT/PET, endoscopic ultrasound, and endoscopic mucosal resection should be used to ensure accurate TNM classification (18-20). Following appropriate patient selection, surgical intervention can provide a durable treatment option, but regardless of the operative approach chosen, the need for R0 resection takes precedent as positive surgical margins confer a worse prognosis (21).

Surgery for EC

Cervical EC

Esophageal surgery for the management of EC can be divided into anatomic regions. The management of cervical disease can be considered a functionally separate process which can require additional considerations given the physical proximity to structures such as the larynx. The use of neoadjuvant therapy (22-24) as well as pharyngo-laryngo-esophagectomy (PLE) (25,26) is beyond the scope of this article.

Mid/Distal EC

Ivor Lewis esophagogastrectomy (ILE)

Originally described by the Welsh surgeon Ivor Lewis in 1946 as a 2-staged procedure (27), the modern iteration of the eponymous operation consists of a single stage procedure utilizing both a laparotomy as well as a right thoracotomy. The abdominal incision allows conduit creation, which most commonly involves careful mobilization of the stomach and preservation of the right gastric and gastroepiploic arteries. The right thoracotomy allows for an upper thoracic anastomosis following resection of the involved portion of esophagus (28). This combined approach utilizing a thoracotomy and a laparotomy also allows for a two-field lymphadenectomy.

Transhiatal esophagectomy (THE)

The first cadaveric esophagectomy without a thoracotomy was described by the German anatomist Denk in 1913 and the first attempt in humans was performed in 1933 by British surgeon Turner (29,30). The modern application of this approach came to light in 1976 by Orringer (31) and utilizes abdominal and cervical neck incisions. A majority of the esophageal dissection is performed through the hiatus via the abdominal incision. The cervical incision allows for dissection of the proximal-most esophagus. The stomach conduit is constructed and then manipulated through the hiatus and brought to the neck where the esophagogastric anastomosis is constructed (32). This approach has been applied to malignancies in both the mid and distal esophagus, however larger mid-esophageal masses and/or masses in close approximation to the tracheal airway may not be best served by this approach (14). With the THE, only an abdominal lymphadenectomy can be performed as the thoracic esophagus is blindly dissected through the diaphragmatic hiatus.

McKeown esophagectomy

The "three-hole" esophagectomy was first described by McKeown in 1969 and detailed a 3-incision procedure which was completed in a single stage (33). Unlike the transhiatal approach, the addition of a right thoracic incision allows for a more direct visualization of the esophageal dissection especially in anatomic areas close to the trachea. And although not addressed in the original description, the modern interpretation of the operation also allows for a thoracic esophageal lymphadenectomy (34).

Adequate lymphadenectomy

As discussed, different surgical approaches may alter lymph node accessibility during EC resection. Japanese researchers described recurrence patterns of resected EC in the 1980s and noted that locoregional lymph nodes seemed to play an important role in disease recurrence (35). The adequacy of lymph node removal has been approached in two ways. Many

Asian cohort based researchers have focused on the number of "fields" considered for lymph node dissection, with "two-field" encompassing abdominal and thoracic basins and "three-field" including the cervical esophagus (36). Alternatively other researchers have approached lymphadenectomy in terms of raw lymph node harvest (37).

To date, no definitive recommendation has been made for the number of fields required for adequacy. Recent meta-analyses have attempted to examine a collection of mostly retrospective studies. Ma *et al.* and Ye *et al.* found that a three-field approach may result in better overall survival, however this is at the cost of possibly increased morbidity including recurrent nerve damage and anastomotic leak (36,38). The lack of clear, prospective data has resulted in an ongoing clinical trial which is attempting to address the need for a three-field dissection versus two (NCT01807936).

In terms of lymph node harvest, Rizk *et al.* demonstrated in a retrospective examination of 336 patients that staging was best stratified if a minimum of 18 lymph nodes were harvested and that prognosis could be delineated by three categories of nodal involvement (0, 1–4, >4 nodes) (39). Rizk *et al.* subsequently utilized data from 4,627 patients in the Worldwide EC Collaboration database and recommended target lymph node harvest based on T-classification: 10 nodes for pT1, 20 for pT2, and ≥30 for pT3/T4 (37). Studies overall vary on the exact number of nodes needed for accurate staging and prognostication, however based on this work as well as others, current National Comprehensive Cancer Network (NCCN) guidelines have adopted a recommendation of at least 15 harvested nodes (23,39-41).

More recent studies have suggested that the extent of lymphadenectomy is not only associated with staging but it is also independently associated with overall survival (40,42,43). This is particularly true for early stage tumors, suggesting that EC is not always a systemic disease but indeed there is a phase when the tumor is loco-regional (44).

Transthoracic esophagectomy (TTE) versus THE

Although the utility of surgical resection in early stage EC is well agreed upon, the ideal approach has been a matter of debate. There are generally two categories of surgical approach, one which involves a thoracic incision (McKeown and Ivor Lewis) and one which does not (THE). The question arises whether the use of thoracic exposure allows for a superior oncologic resection while its omission may allow for a less morbid procedure.

Rentz *et al.* used prospectively collected US based data from the Veteran Affairs National Surgical Quality Improvement Program for 945 patients. They found no difference in overall mortality between the approaches (10.0% TTE *vs.* 9.9% THE, P=0.983) as well as no difference in morbidity including respiratory failure, sepsis, anastomotic complications, or mediastinitis (45). Hulscher *et al.* performed a prospective trial in which 220 patients were randomized to TTE or THE. They found that THE was associated with less perioperative morbidity including shorter ICU and hospital stays, fewer pulmonary sequelae, and shorter duration of mechanical ventilation but that there was no difference in survival (median OS 1.8 *vs.* 2.0 years, P=0.38) (46). Although their initial study showed a trend towards improved survival in the TTE arm, a follow-up analysis of 5-year survival showed that there was no benefit (34% THE *vs.* 36% TTE, P=0.71) (47). Chang *et al.* utilized a US Medicare linked Surveillance, Epidemiology, and End Results database to examine 868 patients and noted that THE conferred a 30-day mortality benefit (6.7% *vs.* 13.1%, P=0.009) but that following adjustment for patient and provider characteristics, neither approach differed in 5-year survival (HR 0.95, 95% CI: 0.75–1.20) (48). In 2014, Papenfuss *et al.* examined 1,428 patients from the American College of Surgeons-National Surgical Quality Improvement Project (ACS-NSQIP) database and found no difference in 30-day mortality (2.9% THE *vs.* 4.7% TTE, P=0.095) but that the TTE group required more returns to the operating room and more blood transfusions (14.5% *vs.* 10.9%, P=0.046 and 12.5% *vs.* 8.9%, P=0.032, respectively). Interestingly, Bhayani *et al.* examined 1,568 patients using the ACS-NSQIP as well and found that TTE was associated with increased pneumonia, ventilator dependence, and septic shock (OR 1.47, 1.35, 1.86 and P=0.007, 0.04, 0.001, respectively) but did not identify a mortality benefit (49). Like all population-based studies, these are limited by the administrative nature of data: there are no details on performance status, comorbidities, use of pre-operative chemotherapy, or institutional/surgeon volume. Moreover, these databases were not originally designed to answer questions of surgical technique thus subsequent extrapolation should be approached cautiously.

In our opinion a transthoracic approach allows for a more extensive lymphadenectomy, which seems to be associated with better survival especially in early stage cancer. Therefore, if the patient's physical status allows it and the cancer can still be considered loco-regional (less than eight nodes involved) (44), a transthoracic approach is encouraged. Some of the complications related to a thoracotomy may be avoided with minimally invasive techniques.

Minimally invasive esophagectomy (MIE)

Given the benefits seen from minimally invasive approaches to other surgical procedures, the use of similar techniques began to be applied to surgery of the esophagus (50,51). Minimally invasive approaches generally utilize laparoscopy with the addition of thoracoscopy if a thoracic dissection is planned. Indeed after its initial introduction, the utilization of MIE has continued to rise (52). Luketich *et al.* sought to prospectively evaluate MIE and performed a phase II feasibility trial of 95 patients and found it to have acceptable mortality and morbidity (53). Biere *et al.* conducted a randomized control trial to compare open versus MIE in 115 patients and found that the minimally invasive approach was associated with fewer pulmonary infections in the early post-operative period (54). Three-year follow-up data from the same trial was recently analyzed and noted no difference in overall survival or disease free-survival (55). As other studies are underway to evaluate the long-term benefits of the MIE approach and as more MIE programs are developed around the world, it is important to note that the benefits of MIE are subject to a learning curve and that surgeon and center experience plays a role in patient outcome (56,57).

Outcomes and complications

Much of the historical aversion to the application of esophagectomy likely stemmed from high early mortality rates (58,59). However updated techniques and perioperative management have resulted in a safe and beneficial operation. Yet, the reporting of more modern outcomes have been varied and at times inconsistent resulting in an effort to standardize the data collection and reporting of complications associated with esophagectomy (60,61). Furthermore, the complexity of the procedure and the peri-operative management has led to a national and international trend to centralize surgeons and medical centers who undertake the management of EC and this has in turn resulted in additional improvements of patient outcomes (62-65).

Summary

The management of EC is complex and requires particular experience during every step of treatment including operative and peri-operative care. The late and vague presentation of the disease process can pose a difficult diagnostic and therapeutic situation; however in early stage cancers, complete resection is the only potentially curative treatment. Current clinical investigations as well as ongoing refinements in peri-operative care will be essential in the movement to even further improve EC management and patient outcomes.

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Footnote

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