

Surgical indications and optimization of patients for resectable esophageal malignancies

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ABSTRACT

Esophageal cancer is a devastating diagnosis with very dire long-term survival rates. This is largely due to its rather insidious progression, which leads to most patients being diagnosed with advanced disease. Recently, however, a greater understanding of the pathogenesis of esophageal malignancies has afforded surgeons and oncologists with new opportunities for intervention and management. Coupled with improvements in imaging, staging, and medical therapies, surgeons have continued to enhance their knowledge of the nuances of esophageal resection, which has resulted in the development of minimally invasive approaches with similar overall oncologic outcomes. This marriage of more efficacious induction therapy and diminished morbidity after esophagectomy offers new promise to patients diagnosed with this aggressive form of cancer. The following review will highlight these most recent advances and will offer insight into our own approach to patients with resectable esophageal malignancy.

KEYWORDS

Esophageal cancer; indication for surgery; preoperative optimization; review

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Overview

The American Cancer Society projects that in 2013, 17,990 adults will obtain a diagnosis of esophageal cancer and 15,210 will succumb to the disease. While the incidence of this cancer is relatively low, the long-term prognosis is grim with overall five-year survival rates of 17%. There are, however, promising avenues for further gain—including earlier detection, aggressive adjuvant therapies, greater patient optimization, and augmented surgical prowess in managing diseases of the esophagus. This is supported by the disparity of survival depending upon the stage of the cancer at the time of diagnosis with isolated esophageal disease harboring a substantial survival benefit in comparison to those with distant metastasis (38% and 3% five-year survival, respectively) (1). This considerable difference has empowered

both oncologists and surgeons to work together to uncover the best treatment algorithms with patient-specific paradigms at the forefront of their efforts.

The following review will highlight major risk factors for development of esophageal cancer, recent advancements in the realm of the various imaging modalities utilized in staging, and current trends in medical and surgical management with a focus on patient optimization prior to resection.

Clinical presentation

The unique anatomic structure of the esophagus is the reason most individuals presenting with obstructive esophageal symptoms are diagnosed with advanced disease. Because it lacks a true serosal layer, the smooth muscle of the esophagus can stretch, accommodating a large tumor burden before frank symptomatology is evident. For instance, dysphagia, the most common presenting complaint, is not clinically significant until 50-60% of the esophageal lumen has been comprised by the tumor. Typically, this patient population presents with difficulty in swallowing solid foods which progresses to liquids as the tumor increases further in size. This leads to substantial weight loss, yet another regular complaint in those with esophageal cancer. This baseline state of malnutrition can

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make chemotherapeutic and surgical recovery difficult and the importance of a knowledgeable nutritional team must not be underemphasized (2).

Additionally, patients may complain of painful swallowing (odynophagia) which can further exacerbate the aforementioned anorexia. The root cause of this discomfort is most likely multifactorial, caused in part by overlying ulceration as well as direct mediastinal invasion. A number of respiratory specific findings, while rare, can represent tumor invasion into local structures. For instance, hoarseness is indicative of laryngeal nerve involvement and a recurrent cough generally represents a fistulous communication between the esophagus and the tracheobronchial tree. The combination of symptoms present at diagnosis depends largely upon the location of the tumor along the length of the esophagus and, therefore, is in part dictated by whether or not the tumor represents adenocarcinoma or squamous cell carcinoma.

Adenocarcinoma and squamous cell carcinoma: an overview, including disease-specific risk factors

When discussing cancer of the esophagus, it is crucial to differentiate between the two major subtypes—adenocarcinoma (ACA) and squamous cell carcinoma (SCC)—as the risk factors and disease specific characteristics differ significantly depending upon the cell-line of origin (3-5). While there remains a higher incidence of squamous cell carcinoma worldwide, the occurrence of adenocarcinoma has increased in the past three decades while the former appears to have been stable or slightly decreased (6,7). Although the root cause of this trend is not completely understood, it does correlate with a more thorough understanding of the pathogenesis of esophageal cancer as well as recent advancements in disease detection.

The most thoroughly investigated and significant risk factor for adenocarcinoma is the presence of gastroesophageal reflux disease (GERD) (8). While there have also been associations between morbid obesity, medications that diminish the basal lower esophageal sphincter tone, long-standing tobacco abuse and previous thoracic radiation and the development of cancer, reflux remains the most influential risk factor in the progression to invasive disease (8-13). The basic premise is that reflux disease results in intestinal metaplasia (Barrett's esophagus), which further evolves into dysplasia and eventually includes foci of microscopic or grossly invasive cancer. The biology of this degradation includes alterations in various, universally accepted cancer genes, such as *p53*, *p16*, *APC* and *telomerase*, as well as complex interactions between bile, acid, the *Cdx* gene and the

diagnosis of adenocarcinoma (14-16).

The pathway from normal esophageal mucosa to the appearance of squamous cell carcinoma has not been entirely discerned, but there are, nevertheless, some clear risk factors that have been implicated in the development of SCC. This subtype has been linked both to alcohol consumption and to tobacco abuse, as well as a history of head and neck cancer and previous thoracic radiation. Interestingly, several studies have also established the association between red meat consumption and an increased risk of esophageal SCC, presumably due to the production of *N*-nitroso compounds, which have proven to be carcinogenic in animal models (17-19).

This conversation is not purely academic in nature, as a greater realization of the pathogenesis and biological progression of both SCC and ACA has afforded surgeons and oncologists with an improved understanding of the natural history of esophageal disease, its aggressivity, and its expected response to treatment. There is a general consensus that irrespective of histological tumor type, an R0 resection (microscopically negative margins) and the presence of lymph node metastasis are prognostic factors in patient's undergoing surgical intervention for esophageal cancer (3,20). Historically, the studies which have attempted to further delineate prognosis based on subtype have been divided, with several demonstrating a survival benefit in those with ACA (5,21), several presenting improved outcomes in patients with SCC (22,23), and still others showing no significant difference in either group (24).

As the debate surrounding the true impact of histology on overall survival continues, additional disagreement can be found when examining the response of SCC and ADA to neoadjuvant therapies. A large, single institution series demonstrated that after treatment with similar neo-adjuvant regimens, esophageal squamous cell cancer was associated with a higher rate of pCR than adenocarcinoma (42.8% versus 20%) (25). Cancer histology has been reported to influence post-neoadjuvant prognostic characteristics as well. While the most significant predictor of survival in adenocarcinoma appears to be residual nodal status (26), persistent local disease appears to be the most important element in squamous cell cancer (25). Additional studies have established that after trimodal therapy, patients with ACA frequently had malignant lymphadenopathy in the esophageal specimen, which inevitably results in a shorter time-to-metastasis (4,27,28). A more thorough review regarding the impact of neoadjuvant therapy on overall survival will follow in a subsequent section, but it is valuable to discuss the utility of viewing ACA and SCC as separate but similar entities rather than solely grouping them under the modifier 'esophageal cancer'. While the relevance of these distinctions

to the surgeon might not be initially obvious, preoperative optimization is crucial in order to maximize the overall benefit after an esophagectomy.

Diagnosis and staging

Once definitively diagnosed, a combination of imaging modalities has been utilized to most accurately stage esophageal cancer according to the recommendations of the American Joint Commission on Cancer's 7th edition guidelines, which include its depth of invasion (T), its degree of nodal involvement (N) and its spread to distant sites (M) (29). Accurate staging is instrumental to the treatment team as it dictates which therapeutic approach will become the focus of the management strategy.

Endoscopic ultrasound (EUS) is the preferred mechanism to determine the depth of esophageal invasion with an accuracy of almost 90% (30). Precision in distinguishing between the various 'T' stages becomes critical to the surgical team because advances in radiofrequency and endoscopic therapies have afforded patients with dysplastic disease as well as early stage, superficial esophageal cancer (Tis and T1a disease, respectively) an alternative to radical esophagectomy (30-34). Furthermore, local invasion of unresectable structures such as the aorta, vertebrae and the trachea (T4b) excludes surgery as a feasible treatment option. Due to it being widely accepted that the number of positive nodes in the esophagectomy specimen is prognostic of overall survival, it is also essential that imaging be sensitive enough to accurately detect suspicious lymphadenopathy (29,35). Accordingly, in order to be assured of the nodal status preoperatively, an array of information is obtained from EUS, CT, and PET/CT. Aside from merely offering a mechanism for staging, these tools can dictate whether a lesion is amenable to surgical resection. Positive, or highly suspicious, nodes outside of the typical resection field as well as distant sites of metastasis (M1 disease) denote incurable disease with very poor long-term prognosis (1).

Approach to treatment: the interplay of neoadjuvant, endoscopic and surgical therapies

As mentioned previously, individuals with esophageal cancer typically seek medical attention once the disease has progressed to a more advanced stage, resulting in a treatment strategy of which a multi-modal approach is central (36,37). Patients must be carefully analyzed by the surgery, gastroenterology, and oncology services to determine which therapy, or therapies, will be the foundation of this stage-specific approach.

High grade dysplasia (carcinoma in situ)

The risk of progression from high grade dysplasia (HGD) to invasive cancer has been estimated at 10% per year (38). Historically, esophagectomy had been recommended for patients with areas of HGD because it had been associated with a 40-60% risk of harboring cancer (39). More recent investigations, however, have questioned the need for such aggressive treatment in this population of patients, and have demonstrated instead, that radiofrequency ablation (RFA) provides adequate eradication in those with both high- and low-grade dysplasia (90.5% and 81.0%, respectively) (33). Furthermore, in one large study, only 3.6% of patients had disease progression after ablation therapy and an even small number (1.2%) developed cancer (33). Of note, RFA should be avoided in patients with long segments of dysplasia, nodular features or multifocal disease, since these characteristics have been associated with failure of endoscopic treatment.

Stage I disease

As stated above, superficial lesions involving the lamina propria (T1a) without extension into the submucosa (T1b) are typically responsive to endoscopic mucosal resection (EMR) with five-year survival rates above 90% (30-32,34,40,41). This is attributable to the low rate of lymphatic involvement associated with these early stage tumors (42,43). EMR offers a lower-risk alternative to surgical intervention in applicable tumors with complication rates quoted in some studies to be as low as 7% while simultaneously maintaining similar long-term survival as esophagectomy (44,45). The use of endoscopic therapy is cautioned however, in cancers that have invaded beyond the lamina propria (T1b) as locoregional control can be compromised due to a substantial risk of lymph node involvement. These patients, given they have no appreciable metastases, should be referred for a formal resection with lymph node dissection.

Stage II and III disease

The ultimate goal and interest of the surgeon, however, is being able to select which patients will benefit from surgical resection in terms of overall survival and which ones will not. Consequently, patients with advanced, but resectable, lesions should be presented at multi-disciplinary cancer conferences (MDCCs) in order to ensure that the treatment plan follows the most up-to-date and widely accepted guidelines. Several studies have outlined the benefits of MDCCs in patients with

Table 1. A select number of randomized-controlled trials on the benefit of induction therapy followed by surgery vs. surgery alone in the management of esophageal cancer.

References	Publication	Methods	Results
Bosset et al. (53)	NEJM 1997	282 patients: 139—surgery alone 143—induction CRT	No difference in overall survival Chemoradiotherapy resulted in: longer disease free survival (P=0.003) longer interval free of local disease (P=0.01) lower rate of cancer-related deaths (P=0.002) higher rate of curative resections (P=0.017)
van Hagen et al. (52)	NEJM 2012	366 patients: 188—surgery alone 178—induction CRT	Chemoradiotherapy resulted in: greater incidence of R0 resection (P<0.001) longer overall survival (P=0.003) greater median disease free survival (P<0.001)
Walsh et al. (54)	NEJM 1996	113 patients: 55—surgery alone 58—induction CRT	Chemoradiotherapy resulted in: greater median overall survival (P=0.01) greater 3-year survival advantage (P=0.01)
Burmeister et al. (37)	Lancet Oncol 2005	256 patients: 128—surgery alone 128—induction CRT	No difference in overall survival No difference in progression-free survival Chemoradiotherapy resulted in: greater incidence of R0 resection (P<0.001) fewer positive lymph nodes (P=0.003)

Abbreviations: NEJM, New England Journal of Medicine; CRT, Chemoradiation therapy.

esophageal cancer which include enhanced staging (and thus a greater percentage of patients foregoing esophagectomy in favor of endoscopic therapy), an improvement in the time interval from diagnosis to commencement of treatment, and most importantly, a favorable impact on five-year survival (46-48).

These conferences refer to the National Comprehensive Cancer Network (NCCN) guidelines for esophageal cancer as a framework from which to construct their specific intervention. T1b-T4a cancers (tumors invading the submucosa, muscularis propria, adventitia, or specific adjacent structures—pleura, pericardium, and diaphragm) represent resectable disease (49). For those deemed candidates for esophageal resection and especially in T2-T4a and N + (stage II and stage III) disease, preoperative therapy should be considered. This has been supported in several randomized control trials and a large meta-analysis, which have all demonstrated a distinct overall and disease-free survival benefit in individuals undergoing chemoradiotherapy prior to surgical resection (50-52). In the CROSS study, there was a 34% lower risk of death in patients

treated with combined neoadjuvant and surgical therapy in comparison to those who only underwent esophagectomy without any prior systemic therapy (52). There is always the theoretic concern that radiation-induced fibrosis will complicate an ensuing resection, but this was not supported in the aforementioned study as nearly 94% of patients underwent successful esophagectomy following chemoradiotherapy (52). Table 1 provides a brief overview of a select number of the randomized-controlled trials evaluating the benefit of induction chemoradiation therapy.

Stage IV disease

T4b cancers, or those involving the heart, great vessels, trachea or other adjacent organs (e.g., the liver, pancreas, lung and spleen) are not amenable to surgical intervention unless palliation is sought (49). And although there have been several smaller case reports of subsequent metastasectomy in patients with previously resected esophageal cancer primaries, there

have been no large trials that have exhibited a survival benefit in surgically treated Stage IV disease and, currently, it cannot be universally recommended (49,55).

Patient optimization prior to surgical resection

Esophagectomy is an incredibly demanding operation for patients with cancer of the thoracic esophagus and subsequent morbidity is common following resection. It is imperative, therefore, aside from merely selecting the most appropriate treatment strategy, that the surgical team consults multidisciplinary services to perform a thorough preoperative assessment of the patient's cardiac, pulmonary and nutritional reserves.

With gastrointestinal obstruction and tumor cachexia regularly present in esophageal cancer, almost all patients exhibit some degree of malnutrition. There is substantial evidence that malnutrition is immunosuppressive and has a negative impact on survival (56,57). Accordingly, it is generally recommended that placement of definitive enteral access be considered at the time of resection and that patients who are unable to tolerate at least 50% of their goal calories be started on feeds postoperatively (58). While access is usually secured via the jejunum during the esophagectomy, we support the creation of gastric access prior to induction therapy to ensure that preoperative malnutrition is minimized. This can be performed safely via an endoscopic or laparoscopic approach, but careful attention is needed to avoid injury to the gastropiploic artery, which will supply the gastric conduit during reconstruction.

As mentioned above, patients with relatively more advanced disease are typically treated with a combination of induction chemoradiation followed by a definitive resection. Timing of esophagectomy after preoperative therapy has been under scrutiny as there is a delicate balance between allowing patient recovery while also avoiding progression of disease in the interim. Appropriately, several studies have evaluated this time interval and most centers have now adopted a 6-8-week window after induction therapy during which to schedule an esophagectomy.

Surgical options: trans-thoracic, trans-hiatal, and minimally-invasive approaches

Currently, surgical resection remains the only treatment modality with a chance of oncologic cure in patients with more advanced esophageal carcinoma. The operation can be performed either via a transthoracic or transhiatal approach. The most widely used techniques are the Ivor Lewis esophagectomy (ILE), the transhiatal esophagectomy (THE) and the McKeown

esophagectomy. Minimally invasive esophagectomy (MIE) has recently emerged as a cutting edge option for esophageal resection. Using smaller incisions, MIE harnesses the already well-established open techniques while minimizing the physiologic impact of this large-scale operation.

The ILE begins with a laparotomy for conduit construction and mobilization. A right thoracotomy is subsequently conducted for the esophageal and nodal dissection followed by an intrathoracic anastomosis. The McKeown esophagectomy is similar to the ILE however a cervical anastomosis is created via a left neck incision. It is prudent for the surgeon to select a thoracic approach for: tumors abutting the airway or mediastinal vasculature, large middle third esophageal lesions in which a radical resection may prove necessary, patients with suspected mediastinal fibrosis or in patients with prior gastrointestinal surgery which could lead to technical limitations for conduit mobilization to the neck.

THE commences similarly to an ILE with a laparotomy for gastric mobilization and conduit formation while the lymphadenectomy and mediastinal dissection are performed via the diaphragmatic hiatus. The proximal esophagus is subsequently mobilized via a left neck incision and a cervical anastomosis is fashioned. Patients with marginal pulmonary status can benefit from a THE due to the lack of a thoracotomy resulting in a decreased incidence of ventilator dependence and pneumonia (59,60). This is largely attributed to poor pulmonary toileting postoperatively secondary to pain and splinting. Assessing the outcomes of THE versus ILE, the data show that perioperative morbidity and mortality are roughly equivalent. In a 945 patients study, Rentz *et al.*, showed a mortality rate of 10% for ILE and 9.9% for THE (61). Morbidity occurred in 47% of patients following ILE and 49% for THE (61). Risk factors for mortality following an esophageal resection include a serum albumin less than 3.5 g/dL, blood transfusions of more than four units and age greater than 65 (61). There was no difference noted in the incidence of renal failure, infection, pulmonary failure, bleeding or mediastinitis between the two cohorts (61).

Proponents of the thoracic approaches to esophagectomy argue that ILE has been shown to have fewer anastomotic strictures and leaks as compared to THE (62). Moreover it touts a superior oncologic result due to increased exposure, which allows improved visualization of the tumor and the mediastinum resulting in an increased nodal yield as compared to THE. One study showed that ILE collected a mean of 18.5 nodes as compared to 9 for THE (63). Due to the regional lymphatic basins exhibiting a high rate of nodal metastasis, a more substantial nodal yield is important for staging and prognosis. The results of a European randomized study showed that,

although median overall, disease-free, and quality-adjusted survival did not differ statistically between patients undergoing transhiatal or transthoracic esophagectomy, there was a trend toward improved long-term survival at five years with the extended transthoracic approach (64). This subject remains controversial since the benefit of an extended lymphadenectomy is often outweighed by the morbidity of the operation. It has become our practice, however, to utilize a thoracotomy incision or a minimally invasive strategy in most every patient to ensure an adequate lymphadenectomy, with THE being reserved for multifocal or long segment, high grade dysplasia or T1a disease not suitable for EMR.

MIE has now emerged as a safe and feasible operation to offer patients at high volume centers without the need for special selection criteria (65-67). A multitude of studies, including several meta-analyses and a randomized, controlled trial, have reported equivalent mortality rates between MIE and open esophagectomy (OE) (66,68-70). Moreover, MIE has been shown to be associated with a decrease in morbidity, duration of mechanical ventilation, as well as in ICU and overall hospital stay (67-70).

While MIE has demonstrated sound perioperative outcomes, it is also noteworthy that the oncologic impact of the operation is not changed when compared to OE. With improved visualization, the median nodal harvest is higher for MIE than OE (66). Additionally, margin status is similar between the two groups with 87% R0 resections in the MIE group as compared to 92% in the OE cohort (66). Disease free and overall survival following MIE are also similar to its open counterpart, although these data reflect only short term follow-up (65-67). Another benefit to MIE is the enhanced quality of life (QOL) following the operation. Zeng *et al.* showed that following MIE, patients had improved QOL scores, lower pain scores and increased physical function scores (71). Therefore MIE could be the answer for an extensive esophageal and nodal dissection, without the additional morbidity associated with an open, transthoracic approach.

The extent of lymphadenectomy, however, remains a controversial topic. Three field lymphadenectomy, which adds an extensive cervical dissection, is widely advocated by high volume centers in Japan and other countries in the Eastern hemisphere (72-75). Cervical nodal dissection might improve loco-regional control in aggressive upper esophageal lesions, which happen to be more common in these countries (73-75).

However, because the correlation between the three field approach and improved survival is absent, the extended lymphadenectomy has not garnered much support in the West (76). Additionally, there is the concern that a three-field lymph node

dissection merely results in stage migration with the added morbidity of a neck dissection. The number of lymph nodes harvested during esophagectomy is likely more important than the field of dissection. Several studies have demonstrated that a greater number of lymph nodes removed at the time of resection is associated with progressively increased survival. This associated, however, is not linear and is believed to be stronger for locally advanced tumors (77-79). It is, therefore, recommended that a minimum of ten nodes be resected for T1 cancers, 20 nodes for T2 cancers and 30 nodes for T3/T4 cancers in order to maximize 5-year survival.

Conclusions

While the diagnosis of esophageal cancer remains devastating, a greater understanding of the disease's pathogenesis and the impacts of both neoadjuvant and surgical interventions on overall survival have been encouraging. Due to enhancements in the various modalities utilized in esophageal cancer imaging, improved staging has allowed surgeons to select which patient populations will be afforded the greatest benefit after esophageal resection. Similarly, patients with more extensive disease have profited from a combination of more efficacious radiation and chemotherapy prior to their surgical resection. These numerous facets of the treatment platform have been incorporated into multi-disciplinary cancer conferences, which have permitted a rich dialogue between the numerous departments involved in the management of this complex neoplasm. Areas for future investigation include improved screening in high risk individuals, earlier detection by capturing circulating tumor cells or other malignant markers and more personalized treatment paradigms using each individual's unique genomic targets.

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