REVIEW ARTICLE

Outcomes After Surgery for Esophageal Cancer

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ABSTRACT

Esophageal cancer is a virulent malignancy associated with a 5-year overall survival of approximately 5%. Treatment remains controversial—despite the results of prospective, randomized trials of combined-modality therapy—because results are poor with all strategies. The role of surgical resection in patients with esophageal cancer is controversial. The fact that most patients have advanced disease at the time of diagnosis makes surgery futile in the majority of cases. Nevertheless, surgery is the best option for cure in early-stage esophageal cancer and remains the superior modality for local control in locally advanced disease. The benefits and drawbacks of several surgical approaches are discussed in this review. Multiple factors are implicated in the etiology of post-esophagectomy complications, the rate of which is quite high. Perhaps the most important contributor to morbidity and mortality after esophagectomy is the development of pulmonary complications. Over the past decade, there has been a trend toward the increased use of trimodality therapy in potentially operable patients—induction chemotherapy and radiation therapy, followed by surgery. The rationale for using induction therapy is that it allows simultaneous delivery of local (radiation therapy) and systemic (chemotherapy) modalities, provides for early tumor regression and symptom control, results in improved subsequent local control, and identifies responding patients who might benefit from adjuvant therapy. Thus, on the basis of recent studies and meta-analyses, there may be a modest survival advantage for patients who receive induction chemotherapy followed by surgery, compared with surgery alone. There is also an apparent increase in treatment-related mortality, mainly for patients receiving induction chemotherapy and radiotherapy. Currently, National Comprehensive Cancer Network guidelines support the use of induction therapy only in established clinical trial protocols.

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Esophageal cancer is among the 10 most common solid tumors in the United States.[1,2] It is a particularly virulent malignancy that is associated with 5-year overall survival rates of approximately 5%.[2] In the United States, the incidence of adenocarcinoma of the esophagus has increased more rapidly over the past 4 decades than any other cancer.[1,2] The most important risk factor for the development of adenocarcinoma of the esophagus is the presence of Barrett's esophagus (BE),[3,4] which is found in approximately 10% of patients with gastroesophageal reflux.[5]

The presence of BE is associated with an increased risk of adenocarcinoma by a factor of between 30 and 125.[3,6] It is estimated that up to 90% of all adenocarcinomas arise from BE. It has also been demonstrated that symptomatic gastroesophageal reflux, even in the absence of BE, is a risk factor for the development of esophageal cancer.[7] The recent increase in the incidence of esophageal carcinoma and the relationship of esophageal carcinoma to gastroesophageal reflux suggests that the incidence will continue to increase and that esophageal cancer will increase in importance.

Analysis of extent of disease for esophageal cancer is represented by the TNM classification (Table 1), which is based on the premise that a cancer grows locally (T), spreads to regional lymph nodes (N), and eventually metastasizes to distant sites (M), and that this progression is associated with diminishing survival.[8]

The role of surgical resection in patients with esophageal cancer is controversial. The fact that most patients have advanced disease at the time of diagnosis—even if not demonstrable with clinical and radiographic staging—makes surgery futile in the majority of cases. In addition, the morbidity associated with esophagectomy raises concerns about its applicability in most patients. Nevertheless, surgery is the

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best option for cure in patients with early-stage disease and remains the superior modality for local control in patients with locally advanced disease.[9] In order to understand how surgical resection should be employed in patients with esophageal cancer, it is important to understand the fundamental aspects — including risks and benefits — of various esophageal resection strategies.

Table 1. Current TNM staging of esophageal cancer.

TNM classification

T		
	Tis	Carcinoma in situ
	T1	Tumor invading lamina propria, muscularis mucosae, or submucosa
	T2	Tumor invading muscularis propria
	T3	Tumor invading periesophageal tissue
	T4	Tumor invading adjacent structures
N		
	N0	No regional lymph node metastases
	N1	Regional lymph node metastases
M		
	M0	No distant metastases
	M1a	Upper thoracic tumors metastatic to cervical nodes
		Lower thoracic tumors metastatic to celiac nodes
	M1b	Other nonregional lymph node metastases or distant metastases

Stage groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	N0-1	M0
Stage IVA	T1-4	N0-1	M1a
Stage IVB	T1-4	N0-1	M1b

ESOPHAGECTOMY: SURGICAL OPTIONS

General Considerations

Esophagogastrectomy (EG) is associated with considerable morbidity and mortality.[10] While advances in perioperative management strategies have improved early morbidity, complications of EG continue to be appreciably higher than other similarly complex operations, such as pancreatectomy, gastrectomy, and hepatectomy. Furthermore, as the average 5-year survival for esophageal cancer patients is still only 25%, the deleterious effects of surgical complications on quality of life cannot be overstated — especially in the context of a limited life expectancy.

Various surgical approaches may be employed for esophageal resection. Factors involved in the choice of procedure may include disease stage, the location of the primary tumor, patient-related factors (age, previous surgical history, pulmonary function), and the preferences of the surgeon. In general, a proximal margin of 10 cm and a distal margin of 5 cm should be achieved; thus, the location of the tumor is an important determinant of the surgical approach.[11]

In addition, the optimal location of the anastomosis has been debated (cervical vs. thoracic). Advantages of the cervical anastomosis include more extensive resection of the esophagus, the possibility of avoiding thoracotomy, less severe symptoms of reflux, and less severe complications related to anastomotic leak. Advantages of the thoracic anastomosis include a lower incidence of anastomotic leak and a lower stricture rate.[10]

The extent of lymphadenectomy associated with surgical resection has also been debated. Proponents of the radical or "three-field" (cervical, thoracic, celiac) approach report that surgical staging and local control rates are improved.[12] Advocates of the transhiatal approach (in which a cervical and celiac lymph node dissection may still be performed) have demonstrated that overall survival is equivalent and that overall morbidity is reduced.[13,14]

Although some surgeons prefer the colon interposition, most surgeons use the stomach as the conduit to replace the esophagus after EG. The use of the gastric conduit simplifies the procedure, and is associated with equivalent patient satisfaction and fewer postoperative complications. Colon interposition is usually reserved for patients who have had previous gastric surgery or other procedures that have devascularized the stomach. Either the left or right colon may be used, and the colon may be positioned as either isoperistaltic or retroperistaltic.

Ivor-Lewis Esophagogastrectomy

Ivor-Lewis esophagogastrectomy (ILE) involves abdominal and right thoracic incisions, with upper thoracic esophagogastric anastomosis (at or above the azygos vein).[15] Mobilization of the stomach for use as the conduit is performed, with dissection of the celiac and left gastric lymph nodes, division of the left gastric artery, and preservation of the gastroepiploic and right gastric arteries. This approach should be reserved for lesions in the distal esophagus, as margins may be inadequate for tumors in the middle esophagus.

Transhiatal Esophagogastrectomy

Transhiatal esophagogastrectomy (THE) is performed using abdominal and left cervical incisions.[13,15] The mobilization of the stomach for use as the conduit is performed as in the ILE procedure. The majority of the dissection of the esophagus, which is performed through the hiatus, is accomplished under direct vision if retraction is optimized. Visualization and control of segmental esophageal vessels dramatically reduces blood loss and the need for transfusion. The cervical esophagus is mobilized through a limited cervical incision (with preservation of the left recurrent laryngeal nerve) and is transected at the thoracic inlet. Esophagectomy is completed via the abdominal incision and the gastric conduit is drawn through the mediastinum and exteriorized in the cervical incision for the esophagogastric anastomosis. This approach may be used for lesions at any thoracic location; however, transhiatal dissection of large, middle esophageal tumors adjacent to the trachea is difficult and may be hazardous. These tumors are best managed with a three-incision approach.

McKeown (Three-Incision) Esophagogastrectomy

The McKeown (three-incision) esophagogastrectomy approach begins with a right thoracotomy for mobilization of the esophagus and complete thoracic lymph node dissection.[15] In contrast to THE, this dissection is done under direct vision, allowing more precise dissection in cases where the tumor is large, lymphadenopathy is present, or the tumor is in proximity to the airway. This component may also be performed thoracoscopically. Following thoracic dissection, the abdominal and left surgical approaches are performed with the patient in the supine position.

The McKeown approach is particularly suited to mid esophageal tumors requiring extensive dissection. The cervical anastomosis allows for better margins than would be possible using ILE; in addition, the management of cervical anastomotic issues tends to be easier than the management of thoracic anastomotic problems.

Left Thoracoabdominal Esophagogastrectomy

Left thoracoabdominal esophagogastrectomy (LTE) employs a contiguous abdominal and left thoracic incision, through the eighth intercostal space.[15] Mobilization of the stomach for use as the conduit is performed as above and esophagectomy is accomplished via the left thoracotomy. The esophagogastric anastomosis is performed in the left chest, usually just superior to the inferior pulmonary vein, although it may be performed higher if the conduit is tunneled under the aortic arch. This approach may be used for lesions in the distal esophagus or cardia tumors requiring extensive gastric resection.

Minimally Invasive Esophagectomy

The term "minimally invasive esophagectomy" (MIE) encompasses strategies that combine laparoscopic mobilization of the gastric conduit (and the other abdominal components of the procedure) with complete laparoscopic esophageal mobilization and cervical anastomosis, with thoracoscopic mobilization of the esophagus and cervical anastomosis, or with thoracoscopy (or limited thoracotomy) for a thoracic anastomosis.[16] While this approach is feasible and may offer cosmetic advantages, there have been no demonstrated advantages in other outcomes (such as length of stay, postoperative pain, return to full activity, or overall complications) as have been demonstrated with other minimally invasive thoracic procedures. Drawbacks include a considerable learning curve and longer procedure length. An ongoing clinical trial may address these issues.

Transthoracic Esophagectomy vs. THE: Morbidity and Mortality

While there are several approaches to esophagectomy, several specific issues merit focused attention — use of thoracotomy (as opposed to THE or MIE), placement of the anastomosis in the thorax or the neck, and the use of induction therapy (as opposed to surgery alone). Debate continues as to whether THE results in lower morbidity and mortality than transthoracic esophagectomy. To investigate this question from a nationwide multicenter perspective, Rentz et al used the Veterans Administration National Surgical Quality Improvement Program to prospectively analyze risk factors for morbidity and mortality in patients undergoing transthoracic esophagectomy or THE from 1991 to 2000.[17]

Overall mortality was 10.0% for transthoracic esophagectomy and 9.9% for THE (P = .983). Morbidity occurred in 47% of patients after transthoracic esophagectomy and in 49% of patients after THE (P = .596). Risk factors for mortality common to both groups included a serum albumin value of less than 3.5 g/dL, age greater than 65 years, and blood transfusion of greater than 4 units ($P < .05$). When comparing transthoracic esophagectomy with THE, there was no difference in the incidence of respiratory failure, renal failure, bleeding, infection, sepsis, anastomotic complications, or mediastinitis. The authors concluded that there were no significant differences in preoperative variables and postoperative morbidity or mortality between transthoracic esophagectomy and THE.

In another study, 220 patients with adenocarcinoma of the mid to distal esophagus or adenocarcinoma of the gastric cardia involving the distal esophagus underwent either THE or transthoracic esophagectomy with extended en bloc lymphadenectomy.[14] Perioperative morbidity was higher after transthoracic esophagectomy, but there was no significant difference in operative mortality. Median overall, disease-free, and quality-adjusted survival did not differ statistically between the groups.

In summary, there appears to be no difference in early or long-term survival between the two procedures, but there may be an advantage for THE in terms of operative morbidity.

OUTCOMES AFTER ESOPHAGECTOMY

The most significant technical complication of surgical therapy is an anastomotic leak. Ercan et al recently compared outcomes after stapled cervical anastomosis compared to hand-sewn.[18] At 30 days, freedom from cervical wound infection was 92% for stapled vs. 71% for sewn anastomoses (P = .001); freedom from cervical anastomotic leak was 96% vs. 89% (P=.09), respectively. Other hospital complications occurred in 58% and 49%, respectively (P = .17). Other complications include the development of anastomotic strictures requiring dilatation, pneumonia, temporary or permanent vocal cord paralysis secondary to injury of the recurrent laryngeal nerve, and dumping syndrome. The 30-day operative mortality ranges from 3% to 16%.[10]

Risk Factors for Postsurgical Complications

Improvements in perioperative care, surgical techniques, and anesthetic techniques have lead to consistently decreased complication rates, but esophagectomy remains a formidable operation. Many analyses have been performed to identify the most important risk factors for esophagectomy.[19–25] Multiple factors are implicated in the etiology of postesophagectomy complications. For instance, high-volume centers of esophageal surgery have consistently reported significantly lower complication rates than low-volume centers,[26] and patients of high-volume surgeons experience better outcomes than those of low-volume surgeons.[27]

Several well-designed studies have investigated which variables most likely predict complications after EG. Using the Department of Veterans Affairs National Surgical Quality Improvement Program database, Bailey et al recently evaluated nearly 1,800 patients before and after EG and related preoperative, intraoperative, and postoperative variables with morbidity and mortality.[19] Factors independently associated with postoperative complications included induction therapy, diabetes, increased age, and intraoperative blood transfusions, among others. Another study retrospectively reviewed 269 EG patients by multivariate analysis of 30 preoperative and 18 postoperative variables, concluding that the most accurate model for predicting overall mortality comprises age, intraoperative blood loss, and postoperative requirement for inotropic support and respiratory complications. Similarly, Bartels et al found that a composite score — incorporating preoperative functional status, and cardiac, respiratory, and hepatic function — was more accurate in predicting mortality from EG than was assessment of the individual factors.[20]

These efforts, however, have produced few practical suggestions for altering the manner in which EG is approached, except to stratify risk. Furthermore, only Bartels et al have demonstrated beneficial application of risk stratification; no other reports have verified the usefulness of these data toward improving patient outcomes.[20]

Pulmonary Complications

Perhaps the most important contributor to morbidity and mortality after esophagectomy is the development of pulmonary complications.[10,28–33] Other factors have been demonstrated in individual studies to be associated with increased mortality after esophagectomy, including age, atrial fibrillation, surgical approach, extent of resection, genetic and immune factors, nutrition, the use of induction therapy, and pain management[10]; however, the importance of these factors varies across studies, with the exception of age.[34]

Several factors have been associated with pulmonary complications after esophagectomy, including issues related to the preoperative status (age, nutritional status, induction therapy, baseline pulmonary function, ethanol use, smoking history, poor performance status), intraoperative details (stage/location of tumor, surgical approach, estimated blood loss, length of surgical procedure, entry into two separate body cavities, disruption of bronchial innervation, lymphatic circulation), and postoperative details (pulmonary toilet, vocal cord paralysis or recurrent laryngeal nerve palsy, postoperative respiratory muscle dysfunction).

Atkins and colleagues performed a study to determine current morbidity and mortality for EG in a consecutive series of patients using multiple modern resection techniques. Preoperative, procedural, and postoperative variables were statistically related to postoperative mortality to identify the greatest influences on short-term results. The influence of preoperative comorbidities on postoperative morbidity and mortality was based on the Charlson score, a comorbidity index incorporating individual factors on a weighted basis. In this manner, diagnoses more likely to be associated with postoperative morbidity are given progressively higher point values.

Mortality for EG in this series was 5.8% (22/379). However, 64% of patients (200/379) experienced at least one complication following EG. The mean intensive care unit stay was 4 days (range, 0–139 days), while the mean hospital length of stay was 15 days (range, 5–149 days). The median length of stay was 10 days, and 74.9% of patients were discharged from the hospital within 14 days of EG. When preoperative, procedural, and postoperative variables were analyzed by univariate means, age as a continuous variable ($P = .003$), anastomotic leak ($P = .03$), pneumonia ($P = .0005$), Charlson comorbidity index score ≥ 3 ($P = .05$), and swallowing scores of 3 or 4 ($P = .012$) were each associated with increased mortality following esophageal resection. However, when evaluated by multivariable analysis, only age ($P = .002$) and pneumonia ($P = .0008$) were independently associated with mortality. In fact, the development of pneumonia was associated with a 20% incidence of death, compared with a 3.1% incidence of death among patients free of pneumonia. Pneumonia was the principal cause of death in 12 of the 22 (54.5%) patients who died, and respiratory failure secondary to pneumonia was prominent in 18 of the 22 (81.8%) deaths.

Finally, postoperative barium esophagography studies were evaluated and graded on a scale ranging from a normal study (n = 252), to delayed gastric emptying (n = 44), to frank aspiration (n = 38), or leak (n = 35). Patients with a normal swallow study or delayed gastric emptying developed pneumonia in 8.8% of cases, while 38.6% of patients with swallow studies showing aspiration or leak developed pneumonia. Patients who developed pneumonia had significantly worse swallowing studies compared with those patients who were free of pneumonia.

Similarly, Dumont et al also noted that two thirds of all fatal complications were respiratory in nature.[29] In the Avendano study of 61 patients after esophagectomy, all patients who died postoperatively developed pneumonia.[28] Kinugasa et al found that development of pneumonia after esophagectomy was associated with worse prognosis for overall survival ($P < .01$), along with pathologic tumor stage; they showed recently that those with pneumonia had 26.7% 5-year survival while those without pneumonia had 53.4% survival at 5 years.[31]

One of the most consistently proven preoperative factors associated with postoperative pulmonary morbidity is advanced age. Sauvanet et al showed that pulmonary morbidity was associated with age greater than 60 years.[24] Kozlow et al also show strong association between aspiration pneumonia and age.[35] In addition, advanced age has also been shown to be an independent predictor of mortality after esophagectomy.[10,19,32]

Although it has been demonstrated that patients subjected to esophagectomy who are older than 70 years have significantly higher rates of pulmonary complications, mortality for elderly patients undergoing esophagectomy has decreased considerably over the past 2 decades[36] and esophagectomy can be performed safely in the elderly population.[34] Elderly patients, particularly those with significant esophageal disorders (including malignancy and end-stage benign disorders of the esophagus), are more likely to have underlying, subclinical swallowing disorders that may predispose them to postoperative complications such as aspiration and pneumonia. Therefore, it seems that the best approach for the elderly patient with resectable esophageal disease is to recommend surgery (provided the patient is physiologically able to tolerate the procedure), keeping in mind the attendant risks.

MANAGEMENT OF BARRETT'S ESOPHAGUS WITH HIGH-GRADE DYSPLASIA

The treatment of patients with BE and high-grade dysplasia (HGD) is controversial. Esophagectomy has been considered the treatment of choice in operable patients due to the risk of subsequent development of carcinoma (prophylactic), as well as the risk of unrecognized cancer due to sampling error in endoscopic biopsies (therapeutic). In a study of 15 patients with a preoperative diagnosis of BE with high-grade dysplasia only who underwent EG, the final pathologic study demonstrated carcinoma in situ in 3 patients (20%) and invasive carcinoma in 8 patients (53%).[37] A meta-analysis of published results of 119 patients undergoing resection demonstrated an incidence of invasive cancer rate of 47%, an operative mortality of 2.6%, and a 5-year survival in patients with invasive carcinoma of 82%.[37] Thus, a substantial percentage of patients with BE and high-grade dysplasia already have invasive carcinoma at the time of diagnosis.

As with BE and low-grade dysplasia, the options of photodynamic therapy[38] and radiofrequency ablation[39] may be considered. Unlike resection, each of these minimally invasive techniques has an associated treatment failure rate. Of particular concern is the risk of residual columnar cells becoming embedded in the squamous re-epithelialization process, preventing visualization at surveillance biopsy.

MANAGEMENT OF ESOPHAGEAL CANCER

Evidence-based guidelines and stage-specific therapy should be employed to optimize outcomes.[9] Esophageal cancer treatment remains controversial—despite the results of prospective, randomized trials of combined-modality therapy—because results are poor with all strategies. Successful treatment of esophageal cancer must include therapy for local control (surgery or radiation therapy) and effective systemic therapy (which has not been developed to date).

Improving Preoperative Staging

Staging studies are performed to assess prognosis and determine therapy. Computed tomography (CT) can determine the location and extent of the primary esophageal tumor, including local invasion of the mediastinum, tracheobronchial tree, aorta, and pericardium. Furthermore, this test can evaluate the mediastinum for lymph node involvement and exclude metastases in the liver, adrenals, and brain.

Positron emission tomography (PET) has emerged as a useful study to improve the staging of esophageal carcinoma. Patients with a tissue diagnosis of esophageal carcinoma should undergo PET scanning for evaluation of metastatic disease. This technology has been shown to be effective in identifying metastatic disease in patients with esophageal carcinoma. In a study of 58 patients with esophageal cancer (biopsy-proven), PET identified primary tumors in 56.[40] In this study, 35 patients underwent esophagectomy; 21 were found to have involved lymph nodes, 11 of which were identified preoperatively by PET. Luketich and colleagues evaluated 91 patients with esophageal cancer.[41] In follow-up, 70 sites of metastases were identified in 39 patients; PET detected 51 metastases in 27 of 39 patients. In this study, PET was superior to CT in terms of sensitivity (69% vs. 46%), specificity (93% vs. 74%), and accuracy (84% vs. 63%).

In a prospective study of preoperative staging, Flamen and colleagues compared the accuracy of PET to conventional staging modalities in 74 patients with esophageal cancer.[42] In this study, PET had a higher accuracy for identifying stage IV disease compared to the combination of CT and endoscopic ultrasound (EUS; 82% vs. 64%, respectively). Evaluation with PET led to upstaging in 11 patients (15%) and downstaging in 5 patients (7%).

Endoscopic ultrasound provides five-layer examination of the esophageal wall to delineate tumor depth and examine adjacent structures, especially lymph nodes. It provides the most sensitive characterization of the primary tumor in terms of depth of mural invasion (T status). With EUS, malignant lymph nodes will appear large, round, hypoechoic, and heterogenous, with sharp borders. Benign nodes tend to be small, oval, hyperechoic, and homogenous, with indistinct borders. The overall accuracy for T staging is 84%; assessment is most accurate for T3 and T4 tumors (90%) and there is potential to overstage T1 and T2 tumors.[43]

Endoscopic ultrasound may also be used in the staging of lymph node metastases. Lymph node staging with EUS criteria alone has an accuracy of 84%, a sensitivity of 89%, and a specificity of 75%.[44] Endoscopic ultrasound-guided fine-needle aspiration of suspected lymph nodes improves the accuracy of this technique, and has a sensitivity of 92% and a specificity of 93%.[45] The limitations of T staging by EUS include dependence on the experience of the sonographer and the relative inability to assess obstructing tumors.

Combined-Modality Treatment

Resectable patients with T1/T2 esophageal carcinoma are advised to proceed with surgery.[9] Patients with T3 or N1 disease may be candidates for preoperative chemotherapy and radiation therapy followed by surgery, though induction therapy regimens are recommended only in established clinical trials. Patients with locally advanced disease may receive definitive treatment with chemotherapy and radiation therapy as well. A recent trial assessed chemoradiotherapy with and without surgery in 172 randomly assigned patients with locally advanced esophageal cancer.[46] This study demonstrated equivalent survival, yet the surgical mortality was unacceptably high.

Patients with M1a disease may be considered for induction therapy and surgery, though the majority of these patients are not candidates for surgery. Patients with distant metastatic disease (M1b) may be treated palliatively with chemotherapy, with or without radiation therapy.

Over the past decade, there has been a trend toward the increased use of trimodality therapy in potentially operable patients — induction chemotherapy and radiation therapy, followed by surgery. The rationale for using induction therapy is that preoperative therapy allows simultaneous delivery of local (radiation therapy) and systemic (chemotherapy) modalities, provides for early tumor regression and symptomatic control, results in improved subsequent local control, and identifies responding patients who may benefit from adjuvant therapy.

Compared to surgery alone, induction chemotherapy alone has not been shown to improve survival in all studies. Three large prospective, randomized trials evaluated the use of induction therapy with cisplatin and 5-fluorouracil (5-FU) followed by surgery, compared to surgery alone. Two trials demonstrated that overall long-term survival and median survival were nearly identical in patients treated with induction chemotherapy followed by surgery, compared to surgery alone[47,48]; the third trial demonstrated an advantage with induction chemotherapy.[49]

In a study from Hong Kong, 147 patients were randomized to receive induction therapy (cisplatin and 5-FU) followed by surgery or surgical resection only.[47] The 2-year survival for patients receiving induction therapy and surgery vs. surgery alone was 44% vs. 31% (P = not significant). In an Intergroup study, 423 patients were similarly randomized to receive induction chemotherapy followed by surgery or surgery alone. There was no difference in median survival, 2-year survival, or 4-year survival between the patients who received chemotherapy and surgery vs. surgery alone.[48]

The Medical Research Council (MRC) reported a trial involving patients with potentially resectable esophageal carcinoma.[49] In this trial, 802 patients were randomized to receive induction chemotherapy (two cycles of cisplatin and 5-FU) followed by surgery or surgery alone. At short median follow-up, there was a 3.5-month advantage in median survival (16.8 months vs. 13.3 months) in the patients receiving induction therapy. However, this trial had numerous problems with clinical methodology, including the treatment of 10% of patients off protocol with radiotherapy, the exclusion of patients from China, and a lower than expected median survival in the patients treated with surgery alone. Longer follow-up will be necessary to ascertain if a survival advantage persists.

Cunningham and colleagues recently reported the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial.[50] In this study, patients with resectable adenocarcinoma of the stomach, gastroesophageal junction, or lower esophagus were randomized to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). Chemotherapy consisted of three preoperative and three postoperative cycles of epirubicin, cisplatin, and infused fluorouracil (ECF). As compared with the surgery-alone group, the ECF group had a higher likelihood of overall survival (5-year survival rate, 36% vs. 23%) and progression-free survival. However, only 26% of patients in this trial had carcinoma of the esophagus or the gastroesophageal junction.

Several trials have investigated the use of induction chemotherapy and radiation therapy followed by surgery compared to surgery alone.[48,51-55] In a study by Leprise and colleagues, 86 patients were randomized to receive preoperative cisplatin and 5-FU plus radiation therapy plus surgery or surgery alone.[51] There was no significant survival difference at 1, 2, and 3 years.

A study from Walsh and colleagues focused on the use of multimodality therapy in a subset of patients with adenocarcinoma of the esophagus.[55] In this study, 113 patients with adenocarcinoma were randomized to receive preoperative cisplatin/5-FU with concomitant radiation therapy (40 Gy) plus surgery or surgery alone. Median survival was improved with induction therapy (16 months vs. 11 months; P = .01). There are, however, concerns regarding this study. It is not clear that all patients were staged similarly, and the average delay to surgery was 3 months. The patient withdrawal rate in the combined-modality group was 17%, and 51 other patients (45%) dropped from analysis. The 3-year survival rate of 6% in the surgical arm compares unfavorably with most other studies in the literature; survival in the Intergroup study was approximately 26%.[48]

Bosset and colleagues studied 282 patients with squamous cell cancer of the esophagus randomized to receive preoperative cisplatin with concurrent RT (37 Gy) plus surgery or surgery alone.[53] Complete pathologic response was observed in 26% of the patients receiving combined therapy; however, median survival was 18 months in both groups and there was no difference in 1-, 2-, and 5-year survival. In a study by Urba and colleagues, 100 patients were randomized to receive cisplatin, vinblastine, and 5-FU with concurrent radiation therapy (45 Gy) plus surgery or surgery alone.[52] At a median follow-up of 8.2 years, there is no significant difference in survival between the groups.

Randomized trials comparing induction chemotherapy and radiation therapy followed by surgery compared to surgery alone in patients with potentially resectable esophageal cancer demonstrate conflicting results. In an attempt to clarify the role of induction therapy in esophageal cancer, Fiorica and colleagues performed a meta-analysis of six published randomized trials comparing preoperative chemotherapy and radiation therapy followed by surgery to surgery alone.[56] They concluded that the pooled estimate of treatment effects was statistically significant in favor of preoperative chemoradiotherapy followed by surgery for overall survival. However, they conceded that exclusion of the controversial Walsh trial[55] led to a loss of statistical significance between groups. In addition, the risk for postoperative mortality was higher in the chemoradiotherapy plus surgery group.

Another meta-analysis was performed to determine the effect of preoperative treatment on survival of patients with resectable esophageal cancer and the effect of preoperative treatment on patient mortality.[57] Eleven randomized trials involving 2,311 patients were analyzed, demonstrating that preoperative chemotherapy improved 2-year survival compared with surgery alone; the absolute difference was

4.4% (95% confidence interval [CI], 3%–8.5%). For combined chemoradiotherapy, the increase was 6.4% (nonsignificant; 95% CI, -1.2%–14.0%). Treatment-related mortality increased by 1.7% with neoadjuvant chemotherapy (95% CI, -.9% –4.3%) and by 3.4% with chemoradiotherapy (95% CI, -.1%–7.3%), compared with surgery alone. Finally, another meta-analysis assessed nine randomized trials with a total accrual of more than 1,000 patients.[58] This analysis found that induction chemoradiotherapy followed by surgery was associated with improved 3-year survival and reduced local and regional recurrence, compared to surgery alone.

Thus, on the basis of recent studies and meta-analyses, there may be a modest survival advantage for patients who receive induction chemotherapy followed by surgery, compared with surgery alone. There is also an apparent increase in treatment-related mortality, mainly for patients who receive induction chemotherapy and radiotherapy. Due to the lack of consensus regarding the use of induction chemotherapy prior to surgery in patients with potentially resectable esophageal cancer, the National Comprehensive Cancer Network (NCCN) treatment guidelines support the use of induction therapy only in established clinical trial protocols.[59]

The use of induction regimens increases the toxicity of treatment (as compared to surgery alone). Age is often cited as a reason for not considering preoperative therapy. Rice and colleagues reported their results with preoperative chemotherapy and radiation therapy for esophageal cancer in elderly patients.[60] In this study, 312 consecutive patients underwent esophagectomy for esophageal cancer. Outcomes in patients over 70 years old who underwent preoperative therapy were compared with those of patients younger than 70 who received preoperative therapy. There were no differences in the rates of postoperative cardiac, pulmonary, neurologic, gastrointestinal, or anastomotic complications.

IMPROVING OUTCOMES AFTER SURGICAL RESECTION FOR ESOPHAGEAL CANCER

Surgeon and Hospital Volume

Birkmeyer and colleagues analyzed the effect of hospital volume on outcomes from complex surgical procedures using information from the national Medicare claims database.[26] Mortality decreased as volume increased for all types of procedures analyzed, but the relative importance of volume varied markedly according to the type of procedure. For esophageal resection, adjusted mortality at very-low-volume hospitals was 11.9% higher than at very-high-volume hospitals.[26]

In a subsequent study, the effect of surgeon volume was investigated.[27] In this study, surgeon volume was inversely related to operative mortality for all procedures studied. The adjusted odds ratio for operative death (for patients with a low-volume surgeon vs. those with a high-volume surgeon) varied widely according to procedure. Surgeon volume accounted for a large proportion of the apparent effect of hospital volume, accounting for 46% of mortality for esophagectomy. For most procedures, including esophageal resection and lung resection, mortality was higher among patients with low-volume surgeons than those with high-volume surgeons, regardless of the surgical volume of the hospital in which they practiced.[27]

Molecular Markers

A better understanding of the molecular biology of esophageal cancer will improve patient outcomes in several ways. An established marker or panel of markers may lead to earlier diagnosis in patients with gastroesophageal reflux disease or BE. The use of molecular markers may improve the staging of patients with esophageal cancer in terms of measuring extent of disease and assessing prognosis. Prediction of treatment sensitivity or resistance using molecular parameters will improve the assignment and efficacy of therapy. Finally, molecular and genetic factors may prove to be important targets for biologic therapy.

Several mechanisms of resistance to chemotherapy have been identified among the agents that are commonly used in the systemic treatment of patients with esophageal cancer — paclitaxel, platinum, and 5-FU. A recent study from our laboratory evaluated the initial endoscopic biopsy material from patients who subsequently underwent trimodality therapy, including chemotherapy with cisplatin and 5-FU, radiation therapy, and surgery.[61] Analysis was performed on seven markers of chemotherapy or radiation therapy resistance. In this study, elevated expression of GST-π and P-gp was associated with decreased survival, thus they may be markers of treatment resistance. Expression of erb-B2 was associated with enhanced survival; thus erb-B2 may be a marker of treatment sensitivity.

Another study was performed in an attempt to define the prognostic value of a group of molecular tumor markers in a well-staged population of patients treated with trimodality therapy for esophageal cancer.[62] The original pretreatment paraffin-embedded endoscopic esophageal tumor biopsy material was obtained from 118 patients treated with concurrent cisplatin, 5-FU, and radiation therapy (45 Gy) followed by resection. Three markers of possible platinum chemotherapy association (metallothionein [MT], glutathione S-transferase-π [GST-π], P-glycoprotein [P-gp or multidrug resistance]) and one marker of possible 5-FU association (thymidylate synthase [TS]) were measured using immunohistochemistry. The median cancer-free survival was 25.0 months, with a significantly improved survival for the 38 patients who had a complete response ($P < .001$). High-level expression of GST-π, P-gp, and TS was associated with decreased survival. Multivariate analysis identified high-level expression in two of the platinum markers (GST-π and P-gp) and the 5-FU marker TS as independent predictors of early recurrence and death. Independent prognostic significance was observed, which suggests that it may be possible to predict which patients may benefit most from trimodality therapy.

DISCUSSION

As with most malignancies, thorough, accurate staging, multidisciplinary evaluation, and guidelines-oriented stage-specific therapy are critical to optimizing outcomes for patients with esophageal cancer.[9] Patients with stage T1-2N0 disease are treated with surgical resection alone, while most patients with T3 or N1/M1a disease should be evaluated for induction therapy followed by surgery. Patients who are not considered surgical candidates, for oncologic or physiologic reasons, are considered for chemotherapy and radiation therapy. A spectrum of surgical approaches may be employed, based on factors such as disease stage and location of the tumor. Outcomes after esophagectomy may be optimized by thorough staging, careful patient selection and preparation, and strict attention to the evaluation and management of postoperative complications, particularly pneumonia.[10] In the future, biologic parameters may improve the clinician's ability to select which patients would benefit from surgical resection.[60]

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Disclosures of Potential Conflicts of Interest

Dr. D'Amico indicated no potential conflicts of interest.