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Surgery for Esophageal Cancer

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Esophagogastrectomy

Esophagogastrectomy (EG) is associated with considerable morbidity and mortality.¹ While advances in perioperative management strategies have improved early morbidity, complications of EG continue to be appreciably higher than those of other similarly complex operations such as pancreatectomy, gastrectomy, and hepatectomy. For example, high-volume centers of esophageal surgery have consistently reported significantly lower complication rates than low-volume centers,² and high-volume surgeons have better outcomes than low-volume surgeons.³ Furthermore, the average 5-year survival rate for esophageal cancer patients is still only 25%, and the impact of surgical complications on quality of life cannot be overstated, particularly when considering the limited life expectancy.

Various surgical approaches may be employed for esophageal resection. Factors involved in the choice of procedure may include the stage of the disease, 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 distal margin of 5 cm should be achieved; thus, the location of the tumor is an important determinant of the surgical approach.

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.¹

Atkins and colleagues performed a study to determine current morbidity and mortality rates of 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. The mortality rate of EG in this series was 5.8% (22/379). However, 53% 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 co-morbidity 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 deaths (54.5%), and respiratory failure secondary to pneumonia was prominent in 18 of the 22 (81.8%) deaths.

Management of Barrett's Esophagus with High-Grade Dysplasia

The treatment of patients with Barrett's esophagus (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 esophagogastrectomy, the final pathologic study demonstrated carcinoma-in-situ in three patients (20%) and invasive carcinoma in eight patients (53%).⁴ A metaanalysis of published results of 119 patients undergoing resection demonstrated an incidence of invasive cancer of 47%, operative mortality of 2.6%, and 5-year survival in patients with invasive carcinoma of 82%.⁴ 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 and radiofrequency ablation may be considered.^{5,6} 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.⁷ The treatment of esophageal cancer remains controversial, despite the results of prospective, randomized trials of combined modality therapy, because the 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).

Operable patients with T1-2 esophageal carcinoma are recommended to proceed with surgery.⁷ Patients with T3 or N1 disease may be candidates for preoperative chemotherapy and radiation therapy followed by surgery, or for definitive treatment with chemotherapy and radiation therapy. Patients with M1a disease may be considered for induction therapy and surgery, although 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 distant (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.

The use of induction therapy has not been proved to improve survival in all studies, compared with surgery alone. Two large prospective, randomized trials evaluated the use of induction therapy with cisplatin and 5-fluoururacil (5-FU) followed by surgery, compared with surgery alone. Both trials demonstrated nearly identical overall long-term survival and median survival in patients treated with induction chemotherapy followed by surgery vs. surgery alone.^{8,9} 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.⁸ The 2-year survival of 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 were no differences in median survival, 2-year survival, or 4-year survival between the patients who received chemotherapy and surgery compared with surgery alone.⁹

Several trials have investigated the use of induction chemotherapy and radiation therapy (RT), followed by surgery, compared with surgery alone. In a study by Le Prise and colleagues, 86 patients were randomized to receive preoperative cisplatin and 5-FU + RT + surgery or surgery alone.¹⁰ There was no significant survival difference at 1, 2, or 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.¹¹ In this study, 113 patients with adenocarcinoma were randomized to receive preoperative cisplatin and 5-FU with concomitant RT (4,000 cGy) + 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; the survival rate in the Intergroup study was approximately 26%.⁹

Bosset and colleagues studied 282 patients with squamous cell carcinoma, randomized to receive preoperative cisplatin with concurrent RT (3,700 cGy) + surgery or surgery alone.¹² Complete pathologic response was observed in 26% of the patients receiving combined therapy; however, median survival was 18 months in both groups and there were no differences in 1-, 2-, and 5-year survivals. In a study by Urba and colleagues, 100 patients were randomized to receive cisplatin, vinblastine, and 5-FU with concurrent RT (4,500 cGy) + surgery or surgery alone.¹³ At median follow-up of 8.2 years, there is no significant difference in survival between the groups.

In an attempt to clarify the role of induction therapy for esophageal cancer, Fiorica and colleagues performed a meta-analysis of six published randomized trials comparing preoperative chemotherapy and radiation therapy followed by surgery vs. surgery alone.¹⁴ They concluded that the pooled estimate of treatment effects was statistically significantly in favor of preoperative chemoradiotherapy followed by surgery for overall survival. However, they conceded that exclusion of the controversial Walsh trial¹¹ 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.¹⁵ 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. 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, as compared with surgery alone. There is also an apparent increase in treatment-related mortality, mainly for patients who receive induction chemotherapy and radiotherapy.

A better understanding of the molecular biology of esophageal cancer will improve the outcome of patients 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 commonly used as systemic therapy for patients with esophageal cancer: taxanes, 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.¹⁶ Analysis was performed on seven markers of chemotherapy or radiation therapy resistance. In this study, elevated expression levels of GST- π (glutathione *S*-transferase- π) and P-gp (p-glycoprotein) were associated with decreased survival, and thus may be markers of treatment resistance. Expression of erb-B2 was associated with enhanced survival, and thus 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.¹⁷ 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], GST- π , 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 38 patients who had a complete response ($P<.001$). High-level expression of GST- π , P-gp, and TS was associated with a decreased survival. Multivariate analysis identified high-level expression of 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.

Summary

As with most malignancies, thorough, accurate staging, multidisciplinary evaluation, and guidelines-oriented stage-specific therapy is critical to optimizing the outcomes of patients with esophageal cancer.⁷ In the future, biologic parameters may improve the ability to select which patients will benefit from surgical resection.¹⁶ Patients with T1-2N0 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 operative 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 the 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.¹

References

1. Atkins BZ, Shah AS, Hutcheson KA, et al: Reducing hospital morbidity and mortality following esophagectomy. *Ann Thorac Surg* 78:1170-1176, 2004
2. Birkmeyer JD, Siewers AE, Finlayson EVA, et al: Hospital volume and surgical mortality in the United States. *New Engl J Med* 346:1128-1137, 2002
3. Birkmeyer JD, Stukel TA, Siewers AE, et al: Surgeon volume and hospital mortality in the United States. *N Engl J Med* 349:2117-2127, 2003

4. Ferguson MK, Naunheim KS: Resection for Barrett's mucosa with high-grade dysplasia: implications for prophylactic photodynamic therapy. *J Thorac Cardiovasc Surg* 114: 824-829, 1997
5. Overholt BF, Panjehpour M, Halberg DL: Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. *Gastrointest Endosc* 58:183-188, 2003
6. Bergman JJ, Sondermeijer C, Peters FP, et al: Circumferential balloon-based radiofrequency ablation of Barrett's esophagus in patients with low-grade dysplasia or high-grade dysplasia with and without a prior endoscopic resection using the HALO³⁶⁰ ablation system. *Gastrointest Endosc* 63:AB137, 2006
7. Ajani J, D'Amico TA, Hayman JA, et al (The Writing Committee for the Guideline Panel): Esophageal cancer: clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 1:14-27, 2003
8. Law S, Fok M, Chow S, et al: Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: A prospective randomized trial. *J Thorac Cardiovasc Surg* 114:210-217, 1997
9. Kelsen DP, Ginsberg R, Pajak T, et al: Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 339:1979-1984, 1998
10. Le Prise E, Etienne PL, Meunier B, et al: A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 73:1779-1784, 1994
11. Walsh TN, Noonan N, Hollywood D, et al: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 335:462-467, 1996
12. Bosset JF, Gignoux M, Triboulet JP, et al: Chemotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. *N Engl J Med* 337:161-167, 1997

13. Urba S, Orringer M, Turrisi A, et al: Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal cancer. *J Clin Oncol* 19:305-313, 2001
14. Fiorica F, Di Bona D, Schepis F, et al: Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut* 53:925-930, 2004
15. Kaklamanos IG, Walker GR, Ferry K, et al: Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 10:754-761, 2003
16. Aloia TA, Harpole DH Jr, Reed CE, et al: Tumor marker expression is predictive of survival in patients with esophageal cancer. *Ann Thorac Surg* 72:859-866, 2001
17. Harpole DH, Moore M, Herndon JE, et al: The prognostic value of molecular marker analysis in patients treated with trimodality therapy for esophageal cancer. *Clin Cancer Res* 7:562-569, 2001

Further Reading

Cooper JD: Overview of operative techniques, in Pearson FG, Cooper JD, Deslauriers J, et al (eds): *Esophageal Surgery* (2nd ed). New York, NY, Churchill Livingstone, pp 793, 2002

Ferguson MK, Durkin AE: Preoperative prediction of the risk for pulmonary complications after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 123:661-669, 2002

Greene FL, Page DL, Fleming ID et al (eds): *AJCC Cancer Staging Manual* (6th ed). Philadelphia, PA, Lippincott-Raven, pp 3-8, 91-103, 2002

Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2006. *CA Cancer J Clin* 56:106-130, 2006

Law S, Wong KH, Kwok KF, et al: Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. *Ann Surg* 240:791-800, 2004

Poon RTP, Law SYK, Chu KM, et al: Esophagectomy for carcinoma of the esophagus in the elderly: results of current surgical management. *Ann Surg* 227:357-364, 1996